NUTRITION AND THE CLINICIAN *

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Preventive Nutritional Principles

IN the past two decades academic and consultant physicians have paid increasing attention to diet in medical practice (Brock 1958a). Previously their only real interest in diet after the first five years of life lay in therapeutic diets for the correction of disease. Even then transgressed preventive principles.

Recognition of kwashiorkor as a disease of worldwide importance and the resultant recognition of protein malnutrition aroused the interest of nutritional scientists and public-health administrators but left the clinicians of the temperate and privileged world untouched. The latter have, however, at last been stirred by recent developments in the epidemiology of ischæmic (coronary) heart-disease (I.H.D.). The possibility that this modern epidemic might be partly due to overprivileged eating has had far-reaching effects on the attitude of clinicians to the study of nutrition.

Diet and Ischæmic Heart-disease

Our group has recently expressed its views at some length on this important subject (Brock et al. 1959).

Following the epidemiological work of Keys and Anderson (1954) and others we showed that in the Cape Peninsula our three racial groups had vastly different prevalence-rates for I.H.D. The mortality for our Whites was second only to that of the U.S.A., while in our Bantu the disease is almost non-existent. The mean serum-cholesterol levels at age 40–49 in males were 242 mg. per 100 ml. for the White group and 168 for the Bantu group. The experience of the two groups in respect of diet, especially total, animal, and vegetable fat, exercise, and tension was analysed (Bronte-Stewart et al. 1955, 1956, Keys et al. 1956, Bronte-Stewart 1957). In every respect our Cape Coloured group stood intermediate between the White and Bantu groups. The findings suggested strongly that, whatever genetic factors might underlie the differences in prevalence, the environmental factors mentioned were contributing strongly (Bronte-Stewart et al. 1956). Our hypothesis is that Western privileged culture is operating among these three racial groups to produce high morbidity and mortality from I.H.D. among Whites while the Bantu remain remarkably free (Brock and Gordon 1959), the Cape Coloured group (Brock 1949), who have adopted Western culture for nearly 300 years but have remained underprivileged, have intermediate prevalence. We have evidence that those Bantu who have achieved some material prosperity and become urbanised have higher mean total serum-cholesterol than their rural brethren (Bronte-Stewart et al. 1955) and are beginning to suffer from I.H.D. (Schrire 1958).

We postulate further that Western privileged culture operates through a number of influences including, at least, lack of exercise, "tension", and diet. We are especially interested in dietary modification for those at risk of I.H.D., but feel that knowledge is still too fragmentary for any general application of dietary theories to populations at large. Western privileged diets differ in many ways from primitive rural diets, such as those of the Bantu, but the quantity and quality of dietary fat is of supreme importance in relation to serum-cholesterol levels. Calories derived from fats in the three Cape Town racial groups are Bantu ± 17%, Cape Coloured ± 25%, and European 35–45%.

Diet and Cholesterol Metabolism

It now becomes a matter of great scientific interest and practical dietary importance to determine what fractions of the fats and oils raise and lower serum-cholesterol in man and through what metabolic pathways they act. Taking the second point first, our group (Gordon et al. 1957) has produced evidence that some unsaturated oils in a dose of 100 g. daily increase the excretion of bile acids—the breakdown products of cholesterol—by up to 100% while the serum-cholesterol level falls. The fact that the weight of the stools and the fat content of the fæces do not increase with fæcal bile acids denies a simple laxative mechanism; the bile-acid increase has been confirmed in bile-fistula subjects (Lewis 1958). This could suggest that feeding these oils increases the rate of elimination of cholesterol and its breakdown products.

These findings must be regarded as provisional since fæcal cholic acid is affected by bacterial action. Goldsmith et al. (1959), for example, have reported greater increases from neomycin than from unsaturated oils. The recent report of Avigan and Steinberg (1959) emphasises the complexity of a subject which must be regarded as sub judice.

On the question of which fractions of the fats are effective, Ahrens (1959) has lately reviewed the conflicting evidence. In criticising the essential fatty acid (E.F.A.) hypothesis of Sinclair (1959) and Kinsell et al. (1958) he makes three points: (1) that their definition of E.F.A. is ambiguous in relation to man; (2) that the only chemical structural feature which is common to the oils which reduce serum-cholesterol levels in man is polyunsaturation; and (3) that his group (Ahrens et al. 1959) find corn-oil (rich in E.F.A.) and menhaden oil (almost devoid of E.F.A.) equally efficacious in reducing human serum-cholesterol levels. We agree with Ahrens that there is need to investigate the effects of other qualities of the oils, such as chain length, conjugated double bonds, and presence of trans acids. We have also been interested, with others, in the clues which might be derived from fractionation of those fats which are particularly potent in raising human serum-cholesterol levels. Among these hen's egg yolks are pre-eminent.

Our own clues from recent work can be summarised as follows.

The potency of egg-yolk fat in this respect is different in different species. This could be due to the nature of the bird's customary diet, since it is known that the composition of egg lipid depends on what is fed (Gordon et al. 1958). On fractionation of hen's egg yolk lipid, this activity remains in the acetone-soluble fraction, and further experiments are now in process to determine the precise factor responsible (Bronte-Stewart 1959).

* The second Humphry Davy Rolleston lecture for 1959 delivered before the Royal College of Physicians of London on June 26. The first lecture appeared last week.

The nutritional interest of egg yolk has recently been reviewed in another context (Schjeide and Urist 1959).

The role of dietary fat in human health is the subject of a report by the Food and Nutrition Board of the U.S.A. (1958). Hirsch et al. (1959) have demonstrated how profound may be the alteration in the chemical characteristics of human adipose tissue after prolonged feeding of unsaturated oils. It is difficult to imagine that such profound changes should not affect body metabolism.

Cholesterol and Lipid Metabolism and I.H.D.

The mechanism of the relation between raised serum-cholesterol levels and increased liability to I.H.D. is still obscure. There are two main explanations—i.e., that raised serum-cholesterol levels, or some associated change in blood-lipids, (1) accelerate the formation of atheroma (atherogenesis) or (2) interfere with blood-flow in narrowed or roughened arterial lumina by disturbing the dynamic equilibrium of fibrin formation (thrombogenesis) and fibrin removal (fibrinolysis) or by some other mechanism (e.g., red-cell aggregation).

These two explanations are not mutually exclusive and it is likely that both operate—the first as a long-term process producing atheroma throughout the body, the second as the precipitating mechanism for occlusive thrombosis in atherosclerotic coronary arteries. The research approach towards serum-cholesterol/I.H.D. relationships may of course be quite different according to which of these two hypotheses is being investigated. Our resources are such that we have confined our work to (a) the mechanisms controlling the level of cholesterol and other lipid fractions in the serum and especially the effects thereon of different dietary fats (Gordon 1959), and (b) relations between the serum-lipids, their postprandial reaction to dietary fats, and the mechanisms of thrombosis and fibrinolysis (Merskey and Lackner 1959).

Tentative Dietary Management in I.H.D.

It is clear that we have still much to learn about the relation between dietary fats and I.H.D. I am not personally prepared to make recommendations about dietary fat for populations generally, but I have made a case for applying the principles which we appear to understand to the problem of those " at risk " of I.H.D., through a simple and easily applied diet (Brock 1958b). This diet probably represents a healthy trend anyway and can be combined with other methods of treatment. Its use is also consistent with a broad and critical approach to what is almost certainly a disease of multiple ætiology.

Malnutrition, Undernutrition, and Overnutrition

Reflection on these possible relations between diet and I.H.D. necessitates a revaluation of definitions and concepts in relation to human nutrition. The reader is referred back to the definitions of " nutrients " and " foodstuffs ", and the discussion of the relations between human nutrition and health and disease, in my first lecture (fig. 1). We are now in the position to consider three more terms.

A plea is entered for the use of " malnutrition " in a wide sense to include both overnutrition and undernutrition where these are applicable. The term *dietary malnutrition* should mean an abnormal state of nutrition resulting from wrong eating. It may represent simply an imbalance of nutrients in the diet or it may be associated with the results of excess (overnutrition) or of deficiency (undernutrition) of calories. Calorie requirements have now been defined by an international committee (Food and Agriculture Organisation 1957) in relation to age, sex, physical activity, ambient climate, &c. The results of consumption of an excess or deficiency of calories which leads to a weight either 10% above or 10% below the mean for age, sex, and height can be classed respectively as *dietary overnutrition* and *dietary undernutrition*. These states may in theory result from too much or too little of a well-balanced diet; but in practice, with the exception of the infant at the poorly yielding maternal breast, they are usually associated with nutrient imbalance. In any case, they are forms of " malnutrition " resulting from " wrong eating ".

Long-term Cumulative Effects of Malnutrition

My first lecture discussed the theoretical relations between environmental factors (including diet) and the genotype, in determining constitution, health, and disease. The role of deficiency of vitamins in the ætiology of diseases such as scurvy and pellagra is quite apparent. The role of deficiency and imbalance of aminoacids in the ætiology of kwashiorkor is accepted.

A more far-reaching effect of malnutrition was, however, foreshadowed in several sections of my first lecture. I said that " perhaps the most important effects of malnutrition may be cumulative and manifest themselves through a long-term effect on constitution (fig. 1) with resultant lack of resistance to infection and other stresses and liability to degenerative diseases ". And I pointed out that these cumulative effects are difficult to recognise.

Resistance to Infection

There has been a puzzling contradiction of evidence on the relation of diet to infection. A recent paper by Dubos and Schaedler (1959), however, goes a long way towards a new basis for understanding. They have shown that " the diets most effective in assuring rapid growth of non-infected animals are not necessarily the ones that give the greatest resistance to infection. In other words, the ability to confer resistance is a criterion different from those usually considered by nutritionists ". They point to the variability of different infections as " stresses " and therefore the variability of nutritional state optimal for each type of infection. Their views are illustrated by experiments involving different balances of aminoacids and of fatty acids in the diet. This is of topical importance in view of the stress laid on the same factors in these lectures. Clearly, we have much to learn before we can define the diets most favourable to combating infections in man; but Dubos and Schaedler have at least shown that the effort is well worth while.

Diet and Degenerative Disease

In my first lecture, in considering the geographical pathology of primary carcinoma of the liver and its relation to that of kwashiorkor (protein malnutrition) and of tropical parasitic infestations, I concluded that such infestations could not be more than contributory ætiological factors. I concluded, too, that, though symptomless precancerous cirrhosis in the Bantu could not be a direct or inevitable sequel of kwashiorkor, there were nevertheless strong grounds for thinking that kwashiorkor, and succeeding lifelong milder protein malnutrition, might " condition " or " sensitise " the liver to " cirrhotigens and carcinogens ".

In this second lecture I have drawn attention to the geographical pathology of I.H.D. Recent work has demonstrated conclusively the relation between (a) the quantity and quality of dietary fat and (b) the pattern of lipids in the serum and adipose tissues of man. Geographical pathology

suggests strongly that this pattern may, in turn, be related to I.H.D., through one or both of the mechanisms described as atherogenesis or thrombogenesis. The latter mechanism is likely to be related immediately to dietary fat through the postprandial lipid tide. The former mechanism might account not only for the freedom of races like the Bantu and Japanese from I.H.D. but also for their relative freedom from atheroma of the coronary trunks and aortic arch. In other words, it might be relevant to the problem of atheroma and atherosclerosis throughout the body, and therefore to the phenomena of ageing.

Diet and Stature

In general, privileged populations are taller and heavier than underprivileged ones. This difference is probably in part genotypical but in part environmental. Growth in height, and to a lesser extent in weight, is doubtless under endocrine influence, and this is in part genotypically determined. It is likely, however, that the genotype determines a preferred channel of growth which may be retarded temporarily or permanently by unfavourable environment, including undernutrition and malnutrition, operating through complex pathways of metabolism and endocrine balance. The observed increase in mean height and weight with succeeding generations in privileged populations is probably due to more favourable environment, including better feeding, operating for the first 25 years of life to bring physical constitution towards its preferred or optimum channel. At present, we can only speculate on whether intellectual and emotional constitution is similarly favoured.

Diet, Life Expectation, and Longevity

On the whole, the privileged have greater life expectation than the underprivileged. This is doubtless due to greater application of the favourable influences shown in fig. 1 to be operating continuously on constitution; these of course include good feeding. Is there any possibility that man may suffer from a surfeit of the favourable environmental influences, including good food? There is indeed much evidence, although some of it is indirect. The simplest example is exogenous obesity which undoubtedly reduces life expectation. As I have been saying, the evidence suggests that excess and imbalance of dietary fat may encourage tendencies towards I.H.D. and perhaps towards atherosclerosis in general. The contribution of Dubos and Schaedler (1959) suggests strongly that certain dietary patterns which are favourable for growth may be unfavourable for resistance to infection.

Widdowson and McCance (1959) have been engaged on studies on young animals which suggest that accelerating growth in early life may permanently affect stature and weight. (The effect on longevity is now being investigated.) This hypothesis, although disturbing to pædiatricians, is not inherently unreasonable. Constitution is certainly a product of reaction to stress. There is already a suggestion that the absence of certain stresses in childhood, such as exposure to viruses (e.g., poliomyelitis and infectious hepatitis) may contribute to a constitution which responds in a disastrous way when the virus is met for the first time in adult life. The relation of longevity to protein calories is the subject of a paper by Ross (1959).

Apart from unfavourable effects of overnutrition, can it be that a certain amount of deprivation of food is one of the stresses that lead to useful adaptation in the developing constitution? This is indeed a disturbing thought!

Nutrition and Tropical Parasitic Diseases

Besides the precancerous cirrhosis so prevalent in the Bantu, there are other diseases common in the tropics and described in textbooks of tropical medicine which are also encountered in underprivileged regions outside the tropics. Have we paid enough attention to the role of malnutrition in their ætiology? (Brock 1955).

Idiosyncrasy, Intolerance, and Allergy to Food

Idiosyncrasy, intolerance, and allergy are now the basis of a considerable part of therapeutic dietetics.

Under the heading of food allergy as much harm as good has been done to mankind by the medical profession. In the absence of demonstration of blood reagins, scientific criteria for the diagnosis of food allergy remain sketchy and difficult to apply. Strongly positive intradermal responses to injection of foods must represent an abnormal state, since they do not occur in the majority of people. But to conclude on this evidence alone either that the patient has a food allergy or that his symptoms are due to food allergy is naïve. The difficulties of a critical approach to this subject are discussed by Kessler (1958) and Pratt (1958).

Food intolerance, even in the absence of demonstrable allergy, may be a good reason for eliminating certain items from a patient's diet; but it does not justify attempts at desensitisation. In any case the elimination should be temporary and not made permanent until long periods of observation have shown that the allergy or intolerance is permanent. Great care should be taken—especially in growing children and where there is intolerance to important foodstuffs such as milk—that the missing nutrients are substituted in readily available and palatable alternatives. This is seldom easy, and the personality of the child made " food conscious " may be harmed to a degree which is worse than the symptoms of the condition which is being treated. Food intolerance including food allergy is often temporary and will yield to temporary elimination.

There is an impression that food intolerance and allergy is more common among civilised communities than among underdeveloped peoples. Though unsubstantiated, this suspicion justifies consideration of the extent to which modern processing of food and preservatives may cause development of intolerance or allergy. On this there is at present no satisfactory evidence.

What we need to know are the reasons why apparently healthy children develop intolerance or allergy to common foodstuffs which a healthy child ought to be able to eat. Certainly these reasons include the development of demonstrable reaginic allergy in only a small minority. What can best be called a " nervous temperament " is found in a high proportion but may or may not be in part causative. An undoubted reason in some cases is deficiency of certain enzymes necessary for digestion, assimilation, or metabolism of specific nutrients. Some of these have been carefully studied and identified as genetic deficiencies (e.g., phenylketonuria). The recent advances in enzymology may show this group of causes to be commoner than we have realised. If this is so, we shall have to explain the higher prevalence in privileged people as due to absence of natural selection, and the association with " nervous temperaments " as due to genetic linkage. It will be surprising, however, if some acquired psychosomatic mechanisms are not uncovered and defined.

The whole subject is a challenge to scientific analysis in a field where clinical practice has been characterised by gross empiricism.

Future Concepts

What of the future? Is diet important? The answer is "Of course". Every veterinarian and farmer, when his animals lose condition, looks first to their diet. Doctors and laymen do the same for their pets. Every horse-trainer or rider knows the effect of oats on his horse. Why do oats increase the horse's friskiness and will-to-go? Is it that they improve nutrition? If so, was the basic diet suboptimal, or is this state of friskiness undesirable as a permanent state? Is it that oats act by suggestion? If so, who is suggestible, the horse or the trainer? What lessons applicable to man can we learn from the horse and his oats?

Next, we must ask whether omnivorous man is adaptable to a variety of diets. The answer from history and geography is "Of course". But is there an optimum diet on which he achieves his best performance? What do we mean by "best performance"? Is it in the physical, intellectual, or spiritual realm? What is the health that we are trying to achieve? Is it longevity, usefulness, or happiness?

There are doubtless some lessons to be learnt from the history of man's civilisation. In the early hunting and pastoral days he lived largely on animal and naturally growing vegetable products. When he became more settled, he started the agricultural production of staple carbohydrates. Under conditions of population pressure or where the production of milk was difficult, as in the tropics, he weaned his babies on to starchy paps and gave them *Mehlnahrschaden* or kwashiorkor. I was interested to find that the Bushmen of the Okavango River in southern Africa, who are Stone Age hunters without any agriculture, feed their post-weaning children on a pap prepared from wild legumes and do not have kwashiorkor. But when man advanced again from the starchy paps to the use of cow's milk as a post-weaning food, did he lay early foundations for atheroma? Have we to choose between cirrhosis and primary liver carcinoma on the one hand and the results, on the other hand, of atherosclerosis in our middle to later years?

These are fascinating problems to be solved in the sphere of dietetics. In the meantime, let us acknowledge that orthodox medicine has neglected the role of dietetics in the promotion of health and prevention of disease. In the face of cycles of enthusiasm for one or other cult of the "back to Nature" food faddists, we have resolutely emphasised the adaptability of man to diet. Man is undoubtedly adaptable to a great variety of diets; but almost certainly he has paid a penalty for some of his adaptations. He paid the penalty of *Mehlnahrschaden* and of kwashiorkor for his adaptation to starchy cereals when he left a nomadic life for settled agriculture. He may have paid a further penalty of cirrhosis and primary cancer of the liver in middle age for the same adaptation. He has certainly paid the penalty of obesity, with its attendant discomforts and shortened life-expectation, for the diets of social privilege down the ages, and for the diets of the recent era of plenty among the privileged nations. It seems that he may be paying for these latter diets an added penalty of premature morbidity and mortality from ischæmic heart-disease. Perhaps the cult of moderation in eating (not to mention other pleasures) may have material advantages in health and longevity which outweigh its alleged penalty of smugness.

Behind our attitude to advances in clinical nutrition lurks the spectre of overpopulation. The past two decades have seen in actuality and in potential a vast decline in infant mortality and life expectation. This has resulted from the development of antibiotics and the understanding and correction of undernutrition and malnutrition, especially protein malnutrition in infants. Although rising standards of living eventually lead biologically to falling birth-rates, there is little sign yet in underdeveloped countries—or in some privileged countries, where people ought to know better—of the falling birth-rate which intelligent understanding demands. Very soon, if not already, an average of three children born to each married couple will still result in population increase.

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TRAUMATIC INFARCTION OF THE ANTERIOR LOBE OF THE PITUITARY GLAND

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DISTURBANCES of pituitary function occasionally follow head injury (see Witter and Tascher 1957). It has been inferred in such cases that the pituitary stalk has been severed, since the patients have had signs suggesting loss of function of both the anterior and the posterior lobe of the pituitary gland. Pathological confirmation has been lacking in all but a few instances, and in these few the necropsy was performed long (usually years) after the original injury (Reverchon et al. 1923, Marañon 1926, Schereschewsky 1927, Berblinger 1934, Lerman and Means 1945, Zülch 1950). The usual pathological finding in these cases was a shrunken and fibrotic anterior lobe of the pituitary. Observations on the state of the pituitary stalk have been few and unconvincing, owing to the considerable lapse of time since the injury. Little information is available on the state of the posterior lobe.

We have not been able to find a description of an acute massive lesion in the anterior lobe of the pituitary gland caused by trauma; and we record here five cases in which extensive infarction of the anterior lobe, due to rupture of the pituitary stalk, was found at necropsy shortly after head injury.

A sixth case is recorded which showed the reverse picture—i.e., an anterior lobe without infarction despite a traumatic rupture which had separated the pituitary from the hypothalamus. In this case, however, the site of the rupture was the point of attachment of the stalk to the hypothalamus, and the stalk itself was intact, as also were the arteries which supply the stalk. This unique case is of particular importance in showing that, if the lesion is at a sufficiently high level not to damage the actual stalk, and not to interfere with its blood-supply, infarction of the anterior lobe does not occur.

In all cases the pituitary gland was embedded in paraffin wax and serial sections were cut (in cases 1, 2, 4, and 6 these sections were in the horizontal plane, and in cases 3 and 5 in the sagittal plane). The sections were stained with hæmatoxylin and eosin, iron hæmatoxylin and van Gieson, the periodic-acid Schiff method, and Holmes' silver on-the-slide method.

Case-reports

Case 1.—A man, aged 32, was involved in a motor accident and was admitted to hospital unconscious, bleeding freely from both ears and the nose. There was cyanosis and stertorous breathing. The pupils were wide, with poor response to light. An X-ray of the skull showed a parietal fracture. The blood-pressure was 160/80 mm. Hg. His condition deteriorated and he was treated by hypothermia (32°C) and tracheotomy. Signs of bronchopneumonia developed and he died on the 15th day after the accident.

Necropsy

A linear fracture of the skull was found, extending across the sphenoidal sinus between the left squamous temporal and the right petrous temporal bones. The brain showed moderate grooving of the right uncus, which contained a hæmatoma; slight left cingulate herniation; a right temporoparietal contre-coup injury with underlying softening. Elsewhere there was confluent bronchopneumonia, with staphylococcal abscess formation.

Microscopical examination of the pituitary gland showed an extensive infarct in the anterior lobe (fig. 1). There was a narrow rim of surviving glandular cells over the whole surface of the anterior lobe, and adjacent to the neural lobe there was an area of surviving anterior-lobe cells the extent of which increased slightly towards the inferior part of the gland. The rest of the anterior lobe was infarcted and contained nothing but amorphous cell debris and the ghosts of congested blood-vessels, one of which contained a thrombus. Around the infarct there was a zone of granulation tissue, but few inflammatory cells. The living anterior-lobe cells appeared to be

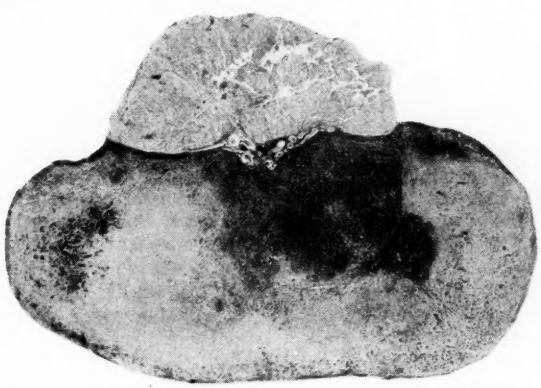

Fig. 1—Case 1: horizontal section through the pituitary gland.

Above (pale) is the posterior lobe. The extensive pale area comprising the greater part of the anterior lobe (below) is completely necrotic (the speckled patch to the left is necrotic, but is dark because of congested vessels). The darker area adjacent to the posterior lobe is composed of surviving anterior-lobe cells. (Hæmatoxylin and eosin. × 6.)

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more loosely disposed than is normal, but for the most part were well differentiated. A few mitotic figures were seen amongst the surviving cells. The neural lobe showed a slight increase in cellularity but no very obvious abnormality. Retraction bulbs were seen in the stump (upper) of the pituitary stalk.

Case 2.—A boy, aged 11 years, was admitted to hospital half an hour after falling from a tree on to the back of his head. A few minutes of initial unconsciousness were followed by a lucid interval of 5 hours during which no abnormal neurological signs were found. He then relapsed into coma. Shortly after the onset of coma he was seen to have a fixed dilated right pupil, with an external squint of the left eye. The legs were extended and toes upgoing. There was marked respiratory embarrassment, and an endotracheal tube was passed. 14 hours after the head injury a right temporal burr-hole was made; a fracture of the skull was found and some extradural clot removed. A fair-sized bony decompression was then made. Later a tracheotomy was done, and he was artificially respired. 2 days after the accident it was noticed that he was passing very large quantities of urine. His plasma-sodium fell to 122 mEq. per litre and plasma-potassium rose to 6·9 mEq. per litre. His blood-sugar rose, and sugar was found in his urine. He died 5 days after the injury, with terminal convulsions.

Necropsy

Necropsy disclosed a transverse basal fracture of the skull, crossing the tuberculum sellæ. The brain was full, the convolutions flattened, and there was a little subarachnoid hæmorrhage around the left Sylvian fissure. There was some herniation through the right temporal skull defect. The pituitary gland appeared normal externally. Apart from tracheitis, bronchopneumonia, and two pints of straw-coloured ascitic fluid, no abnormalities were found. The fixed brain showed a brownish stump representing the upper part of the ruptured pituitary stalk. Coronal sections of the brain showed small ventricles and hæmorrhagic streaks in the right temporal hernia. Apart from fullness there was little else of note in the brain.

Microscopical examination of the pituitary gland showed in the anterior lobe an infarct which was even larger than in case 1, but with essentially the same distribution. The necrotic area was made up of amorphous debris of cells, and in places pyknotic nuclei still remained. The vessels in the necrotic area were congested and were most prominent in the anterior part of the gland. There was virtually no granulation tissue around the infarct and no inflammatory reaction. The area of surviving anterior-lobe cells adjacent to the neural tissue, as in case 1, became more extensive as the sections were traced inferiorly. These surviving cells were not noticeably abnormal. The degeneration of the neural tissue of the posterior lobe could not be adequately assessed owing to damage at necropsy, but this tissue was not necrotic.

Case 3.—A farm labourer, aged 24, was involved in a motor-cycle accident and was admitted after 45 minutes to hospital. He was conscious but confused, passing into deep coma half an hour later, and remaining in coma until he died. Blood was oozing from the right ear and both nostrils. The pupils were dilated and the plantar responses extensor. Breathing stopped after 3 hours, and artificial respiration was instituted. Bitemporal burr-holes revealed subdural clot and lacerated brain, which was sucked out. Artificial respiration was maintained until death, 68 hours after the accident.

Necropsy

At necropsy the skull showed a fracture running from the left superior orbital fissure across the pituitary fossa to the right temporal region. The right tegmen tympani was comminuted. The sphenoidal, frontal, and ethmoidal air sinuses were filled with blood-clot. There was subdural blood-clot up to 0·5 cm. thick in the parietal and occipital regions. Both temporal lobes were lacerated, and there was considerable uncinate grooving. The pituitary gland was surrounded by blood. Elsewhere there was an old left obliterative pleurisy, collapse of the right lung, a small aorta, and some subendocardial hæmorrhages.

On microscopical examination of the pituitary gland almost the whole of the anterior lobe was found to be necrotic. The infarcted tissue showed only the ghosts of cells and fading nuclear remnants. There was a small band of surviving anterior-lobe tissue where the anterior lobe abuts on the neural tissue. There was also a narrow rim of surviving anterior-lobe tissue, only a few cells thick, along most of the surface of the gland and in addition a thin and irregular cuff of surviving cells around the fibrous trabecula. There was no reaction along the borders of the infarct. The changes in the posterior lobe were not striking, apart from a few small hæmorrhages; there was no necrosis here.

Case 4.—A man, aged 31, was in a car which overturned in an accident. He was momentarily unconscious, but was conscious when admitted to hospital, becoming drowsy the next day. A right hemiparesis, extensor plantar responses, and divergent squint developed. Polyuria was noted at this time. Burr-holes made at 24 hours showed a left posterior frontal film of extradural blood. Following this his temperature rose to 105°F, and extensor spasms were noted. A left frontal flap was raised the next day, and a large extradural clot evacuated from the left anterior fossa. No recovery ensued, and he died on the 4th day after the accident.

Necropsy

Necropsy showed a widely sprung coronal suture on the right, with a large fracture of the vault in the frontoparietal area, radiating posteriorly. There was no fracture of the base of the skull. There was a large hæmorrhagic infarct of the left cerebral hemisphere, involving the occipital lobe, inferior temporal and inferior frontal regions, and the thalamus. The hypothalamus and right calcarine cortex were also infarcted. There was a tear of the splenium of the corpus callosum. The pituitary stalk was hæmorrhagic.

Microscopical examination of the pituitary gland showed a moderately large infarct in the anterior lobe involving chiefly its upper part; about a third of the lobe was necrotic. The regions adjacent to the neural tissue were not infarcted. The infarct showed ghosts of cells and remnants of pyknotic nuclei. The neural tissue was not obviously abnormal, apart from a superficial hæmorrhagic area in the lower part of the stalk.

Case 5.—A woman, aged 26, fell off her bicycle and became immediately unconscious. When admitted a few minutes later to hospital she was bleeding from the nose, there was a right proptosis, the pupils were fixed, and a fracture was palpable in the right occiput. There were also jerking athetoid movements of both arms. Artificial respiration in a positive-pressure machine was required, owing to stoppage of breathing; cooling and chlorpromazine were employed. Polyuria (2·5 litres in 24 hours) was noted after 48 hours. She remained unconscious until her death 5 days after the accident.

Necropsy

At necropsy a fracture of the base of the skull was found, which involved both anterior and middle fossæ and passed upwards over the vertex. The fracture line did not involve the pituitary fossa. A left subdural hæmatoma was present. There was tonsillar and uncinate herniation. Contusion and laceration of the left temporal lobe, cerebellar necrosis, medullary hæmorrhage, and a complete midline tear of the corpus callosum were found. Elsewhere there were pleural effusions with pulmonary œdema, subendocardial hæmorrhages, and congested liver and spleen.

Microscopical examination of the pituitary gland showed a massive infarct in the anterior lobe. With the exception of a thin superficial rim (occasionally absent) of surviving cells and a small mass of similar cells contiguous with the neural tissue in the midline, the whole of the anterior lobe was necrotic. Most of the infarct was a homogeneous mass in which the only recognisable structures were faintly outlined blood-vessels, packed with red blood-cells. Some of the vessels, including the artery of the trabecula, contained fresh thrombi. In a few

areas the ghosts of cells and remnants of degenerating nuclei could be seen. No striking changes were seen in the posterior lobe.

Case 6.—A woman, aged 52, fell about 20 feet from a window in an attempt at suicide. On admission to hospital she was comatose, moving all her limbs. There was bleeding from the right ear and the nose and into the nasopharynx. The pupils reacted sluggishly to light and the plantar responses were extensor. She regained consciousness 48 hours after the fall, but later, after recovering consciousness, though she managed to feed herself with difficulty, she was never able to converse. On the 9th day she suddenly lapsed into coma. Subdural blood-clot was removed through biparietal burr-holes, but she remained in coma and died on the 11th day.

Necropsy

At necropsy a fracture of the base of the skull running from the left anterior fossa through the pituitary fossa into the right middle fossa was found. There were in addition a depressed comminuted fracture of the left squamous temporal bone, and fractures of both zygomas and of the left 4th to 7th ribs. The brain showed lacerations of the lateral and orbital aspects of the left frontal lobe, and of the left temporal lobe. The pituitary stalk was obscured by blood-clot; dissection showed it to be completely detached from the hypothalamus, its base resting on the middle of the optic chiasma. There was a slit in the floor of the 3rd ventricle, 0·6 cm. long. The pituitary stalk was still attached to the intact superior hypophysial arteries. There was a midline tear of the optic chiasma. Coronal sections of the brain showed symmetrical ventricular dilatation and infarction of the optic chiasma, the left lower basal ganglia, and the left hypothalamus posteriorly. The lungs were emphysematous.

On microscopical examination of the pituitary gland the anterior-lobe tissues appeared normal, apart from a minute infarct near the anterior border of the gland. The stalk (which had been cut away from the body of the gland before embedding) was cut serially in the sagittal plane. It showed no sign of infarction, but at its upper extremity there were numerous retraction bulbs in the neural tissue.

Discussion

Small, functionally insignificant, infarcts in the anterior lobe of the pituitary gland are rare but are occasionally seen especially in cases of hypertension, raised intracranial pressure, and head injury (Plaut 1952, Wolman 1956, and our own unpublished observations). These small infarcts are not the result of rupture of the pituitary stalk but are presumably due to a very localised cessation of the circulation in only part of the pituitary stalk—e.g., some vessels are subjected to stretching or spasm which stops the blood-flow in a few individual hypophysial portal vessels. In rats we have produced similar small infarcts in the anterior lobe of the pituitary by cauterising individual portal vessels in the pituitary stalk (Daniel and Prichard 1956), thus demonstrating that particular portal vessels provide the sole blood-supply to localised territories of the anterior lobe of the gland.

In five of the cases reported here (cases 1–5) however, the infarct was very large; indeed, in four instances it involved almost the whole of the anterior lobe. Consequently we believe that in these cases the infarction was due to rupture of the pituitary stalk at the time of the accident, although no note on the state of the pituitary stalk was made in the necropsy reports. Our reason for this belief is that the extent and situation of the infarct, together with the distribution of the small areas of surviving anterior-lobe cells, provide a picture which is remarkably similar to that which we have seen in the pituitaries of patients who have survived for only a short time after surgical pituitary-stalk section (Daniel et al. 1958, and unpublished cases). Moreover, we have seen

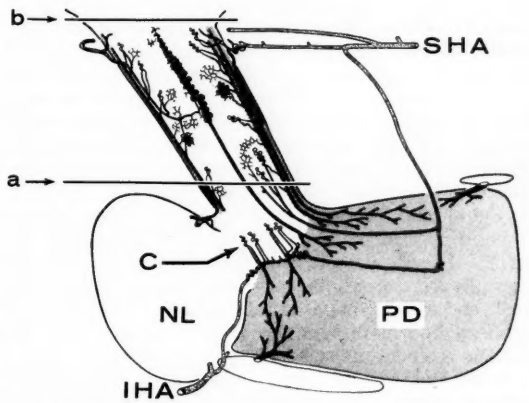

Fig. 2—Diagram of the human pituitary gland in sagittal section showing the blood-supply of the anterior lobe (P.D.).

Transection or rupture of the pituitary stalk low down as at *a* cuts the long portal vessels and thus deprives the greater part of the anterior lobe of its blood-supply. This, however, does not interfere with the blood-flow through the short portal vessels draining the capillary loops, C, in the lower infundibular stem. *b* indicates the level of the traumatic rupture in case 6, and the diagram shows why no infarct developed in the anterior lobe.

N.L., neural (posterior) lobe; S.H.A., superior hypophysial artery; I.H.A., inferior hypophysial artery. (This diagram is modified from fig. 16 of Xuereb et al. 1954b, and further explanations will be found in that paper.)

essentially the same picture of extensive anterior-lobe infarction, with similar small areas of survival, regularly in laboratory animals killed shortly after pituitary-stalk section (Daniel and Prichard 1956, 1957, 1958a and b, Daniel et al. 1959). The distribution of the infarcted and surviving areas is explained by the blood-supply of the various parts of the gland. Both in man and in our laboratory animals the anterior lobe is supplied solely by the hypophysial portal vessels; it has no arterial blood-supply. The greater part of the anterior is supplied by the long portal vessels which arise in and run down the free part of the pituitary stalk (fig. 2). These are inevitably interrupted when the stalk is severed, and thus an extensive area of ischæmic necrosis develops, mainly centrally, in the anterior lobe. A relatively small area of the anterior lobe, adjacent to the neural tissue, survives because this area is supplied by the short portal vessels which arise in the lower infundibular stem (a continuation of the neural tissue of the stalk, which is actually embedded in the anterior lobe) and are thus below the level of the diaphragma sellæ and of the transection (fig. 2 and Xuereb et al. 1954b, fig. 16). The superficial layer of anterior-lobe cells (only a few cells thick) which also survive are presumably kept alive by diffusion from the adjacent highly vascular dura mater. The posterior lobe of the pituitary, on the other hand, gets its blood-supply directly from the inferior hypophysial arteries which arise from the internal carotid arteries below the level of the diaphragma sellæ (Xuereb et al. 1954a). These vessels are not cut when the stalk is severed, and thus the posterior lobe does not become infarcted; it does, however, lose its neural connection with the hypothalamus since the hypothalamo-hypophysial tract is cut.

Our sixth case, in which the anterior lobe of the pituitary was not infarcted, is of great theoretical importance for the evidence which it provides regarding the blood-supply of

the pituitary stalk and the anterior lobe. In this case the pituitary-stalk region was carefully examined at necropsy. The stalk itself was found to be intact and continuous below with the pituitary, but its upper extremity had been torn away from the hypothalamus. As a result of the high level of the tear, the primary capillary bed and the portal vessels within the stalk were undamaged. Moreover the superior hypophysial arteries supplying the stalk were intact. Thus the trauma which had produced separation of the pituitary from the brain had not interrupted the blood-supply to the anterior lobe of the pituitary (see fig. 2). The blood could continue to flow via the superior hypophysial arteries, the primary capillary bed in the stalk, and the long portal vessels in the stalk to the second capillary bed in the anterior lobe, thus preserving the nutrition of both the stalk and the anterior lobe.

As has been shown, transection of the pituitary stalk has different effects on the anterior and posterior lobes of the pituitary gland but seriously impairs the function of both lobes. The anterior lobe undergoes ischæmic necrosis since it loses its blood-supply. The posterior lobe retains its blood-supply but is denervated, losing its neural connection with the hypothalamus. As a result of this denervation of the posterior lobe, diabetes insipidus often develops. Porter and Miller (1948) investigated 5000 cases of closed head injury; in 18 diabetes insipidus had developed, which these workers assumed to be due to damage to the pituitary stalk. The relatively transient nature of the diabetes insipidus in certain cases of pituitary-stalk section may be due to some regeneration of the upper stump of the pituitary stalk, this regenerated neural tissue taking over part of the function of the posterior lobe of the pituitary (Beck and Daniel 1959).

Severe anterior and posterior lobe deficiency occurring together after head injury is rare (Schereschewsky 1927, Maranon and Pintos (1916–18). The diabetes insipidus is often transient or fluctuating. Of special interest in this connection is the case described by Henzi (1952), in which a post-traumatic diabetes insipidus lasted for the rest of the patient's life, from the age of 11 to 60 years.

During this period the patient had seven pregnancies and five normal confinements, and she died finally of a retrobulbar abscess complicating the original head injury. Henzi states that at necropsy there was no sign of a pituitary stalk, and that on section the pituitary was found to be completely separated from the hypothalamus by scar tissue. The posterior lobe was atrophied; the anterior lobe appeared to be normal. There was moderate reduction in the number of cells of the supra-optic and paraventricular nuclei.

The permanence of the diabetes insipidus suggests that the interruption of the supraopticohypophysial tract was complete. In our cases the rapidly fatal issue preclude any observations on this point, but the lesions found provide a pathological basis for the reported post-traumatic signs of hypopituitarism in clinical cases. Probably extensive infarcts of the anterior lobe of the pituitary, such as those described in this paper, are produced only if the transection is through the lower part of the pituitary stalk. Case 6 shows that if the transection is sufficiently high up, the anterior lobe will not become infarcted (fig. 2).

As has already been mentioned, the regular survival of a small area of the anterior lobe adjacent to the neural tissue is due to the fact that section of the pituitary stalk does not damage the blood-supply to this area. There is evidence that in some cases, for reasons at present unknown, the anterior-lobe cells in this surviving area and also those forming the peripheral rim proliferate and grow into the infarcted area; for we have found, both in laboratory animals and in man, that after a considerable time the area of living anterior-lobe tissue may be much greater than it is shortly after operation (Daniel and Prichard 1958a and b, and unpublished observations). Moreover, both in man (as in case 1) and in animals (Daniel and Prichard 1958a) we have seen mitotic figures in cells of the surviving tissue—in some cases in considerable numbers.

It is now generally recognised, largely as a result of the work of Harris (1955a and b), that much of the functional activity of the anterior lobe of the pituitary is controlled by the hypothalamus, which transmits its influence to the gland through the long portal vessels in the pituitary stalk. Since in cases of deliberate stalk section an impenetrable barrier or plate has been inserted between the cut ends of the stalk, the portal vessels cannot regrow, and thus the regenerated anterior-lobe tissue probably has little function, as it cannot re-establish its vascular connection with the hypothalamus. In traumatic cases of pituitary-stalk section, on the other hand, no barrier is necessarily present, although in some cases a fibrous-tissue scar may develop and form a fairly effective obstruction. Without any barrier the severed portal vessels can regenerate and grow down into the surviving parts of the anterior lobe, thus permitting some resumption of anterior-pituitary function. Henzi's (1952) case, in which repeated pregnancies occurred after traumatic pituitary-stalk section, suggests the possibility of resumption of some anterior-pituitary function, despite the presence of a scar-tissue barrier.

The possibility of regeneration both of portal vessels and of anterior-lobe cells may explain why a relatively large proportion of patients show signs of temporary mild hypopituitarism after head injury, although severe post-traumatic Simmonds' disease is rare. It is not, however, generally recognised that mild hypopituitarism may develop after relatively trivial head injury. Moreover the possibility of traumatic pituitary-stalk section should be borne in mind in patients who remain in coma after head injury, once other causes of coma have been excluded.

Summary

Massive necrosis of the anterior lobe of the pituitary gland was found in five cases at necropsy soon after a head injury.

The extensive infarction was considered to be due to transection of the pituitary stalk at the time of injury.

The pathological changes were related to the pattern of vascular supply of the pituitary. Similar massive infarction of the anterior lobe of the pituitary is found both in laboratory animals and in man shortly after operative pituitary-stalk section.

The acute pathological changes in the anterior lobe of the pituitary of man after traumatic pituitary-stalk section have not been described previously.

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CLINICAL AND METABOLIC EFFECTS OF ALDOSTERONE ANTAGONISM

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MOST patients who are accumulating œdema fluid excrete urine with a high content of aldosterone (Axelrad et al. 1955, Duncan et al. 1956, Wolff et al. 1957, 1958). Overproduction of aldosterone by the adrenal gland may be an important factor in œdema formation, and measures which prevent this, or which inhibit the peripheral effects of aldosterone, should lead to sodium loss and potassium retention. The possibility of removing œdema fluid in this way is of clinical importance, because the diuresis would be obtained by a physiological mechanism without potassium or excess chloride loss.

Total adrenalectomy will relieve ascites in patients with hepatic cirrhosis, but only when cortisone-replacement therapy is inadequate (Marson 1954, Guiseffi et al. 1957). Experimental ascites in dogs, produced by constriction of the thoracic vena cava, is associated with high urinary aldosterone excretion, and after total adrenalectomy a diuresis can be obtained by stopping deoxycortone-replacement therapy (Davis et al. 1956).

Amphenone B inhibits the production of many adrenocortical hormones, including aldosterone, and it may increase urine sodium loss in some patients with œdema (Renold et al. 1957, Summerskill and Crabbé 1957, Wolfe et al. 1957). It is too toxic, however, for long-term treatment, and its widespread inhibitory effects limit its use in clinical research (Hertz et al. 1956).

Recently a series of new synthetic steroids has been produced which are reported to antagonise the renal effects of aldosterone and deoxycortone in adrenalectomised rats (Kagawa et al. 1957) and dogs (Liddle 1957), although these compounds are inactive when given alone. Chemically they are characterised by having a spirolactone group on the 17th carbon atom of the cyclopentenophenanthrene ring, the parent compound (SC 5233) being 3(3 - oxo - 17β - hydroxy - 4 - androsten - 17α - yl)-propionic acid γ-lactone. This report describes our experiences with the 19-nor derivative, SC 8109, in two adrenalectomised dogs and in five patients with severe fluid retention.

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Method

Metabolic balance studies were made in all patients. Diets containing 10–27 mEq. of sodium and 35–92 mEq. of potassium were prepared specially and served by one of the hospital dietitians. 24-hour duplicate diets were analysed at the beginning and end of each study. Blood for estimation of plasma electrolytes and urea content was collected at standard times corresponding to each balance period. 24-hour urine specimens and, in cases 1, 4, and 5, 3-day stool collections, were analysed for sodium, potassium, and chloride content by the usual methods. Urine aldosterone extractable at pH 1 was estimated by a method based on that of Ayres, Garrod, Simpson, and Tait (1957) in cases 3, 4, and 5. In cases 2 and 5 the aldosterone secretion-rate was measured by the method described by Ayres et al. (1958).

For the animal experiments two totally adrenalectomised female dogs weighing 25·8 kg. (dog J) and 17·2 kg. (dog M) were used. They were maintained in good health by daily administration of cortisone and 9α-fluorohydrocortisone by mouth. Plasma-electrolyte levels were normal, but in both dogs the blood-urea concentration was higher, and the glomerular filtration-rate lower, than before the adrenal glands were removed.

The studies lasted 6 hours and were made 16 hours after the last meal and 24 hours after the last maintenance dose of steroid, although 25 mg. of cortisone was given by mouth at the start of the experiment. Saline loads were given 2-hourly by stomach tube, and urine was collected by indwelling catheter over 30-minute periods. Injections of *dl*-aldosterone monoacetate were given at the beginning of the experiment by deep intramuscular injection. The spirolactone, either as an oily solution (dog J) or as a microcrystalline suspension (dog M), was administered in two equal intramuscular injections, one 12 hours before the beginning of the study and the other with the aldosterone. The animals are both well trained and tolerate prolonged renal-function studies without distress.

The Patients

Case 1.—*Nephrotic syndrome.* This man, aged 38, developed generalised œdema in April, 1957. He was excreting 25 g. of protein in the urine daily; the serum-albumin level was 1·2 g. per 100 ml., and the serum-cholesterol was 890 mg. per 100 ml. He also had urea retention (blood-urea 80–100 mg. per 100 ml.), mild arterial hypertension (blood-pressure 140/100 mm. Hg), and the urine contained red blood-cells. Since October, 1957, he had been taking chlorothiazide 2 g. daily. At first this produced a good diuresis, but later he became refractory to it. 14 days before the present study was started, chlorothiazide was discontinued; there was considerable dependent œdema, but on a diet containing 12 mEq. of sodium per day his weight was stationary.

Case 2.—*Nephrotic syndrome.* This man, aged 43, developed generalised œdema with ascites in January, 1957. His urine-protein output was 18 g. daily, the serum-albumin level was 1·4 g. per 100 ml., and the serum-cholesterol concentration was 260 mg. per 100 ml. He also had mild urea retention (blood-urea 40–50 mg. per 100 ml.) and his blood-pressure was 150/90 mm. Hg; erythrocytes in the urine were scanty. Treatment with chlorothiazide and sodium restriction was partially successful at first, but his œdema never cleared completely. During a course of dexamethasone his weight increased rapidly and there was severe fluid retention. At the time of the present study he was receiving dexamethasone (3 mg. per day), chlorothiazide (2 g. per day), and a very low sodium diet (10 mEq. per day); on this regime he was losing weight at the rate of about 0·4 kg. per day.

Case 3.—*Chronic congestive cardiac failure.* This was a woman aged 52 who for 7 years had suffered from ascites with generalised œdema due to rheumatic heart-disease. Despite diuretic therapy and rigid dietary salt restriction she required

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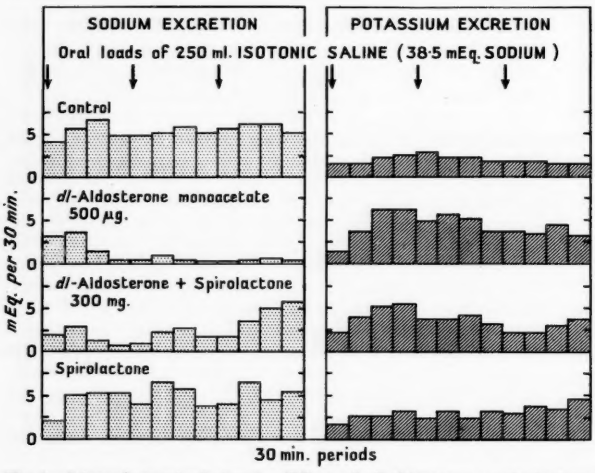

Fig. 1—Adrenalectomised dog J. Effect of *dl*-aldosterone, spirolactone and a combination of the two on the urinary excretion of sodium and potassium.

frequent abdominal paracenteses. At the time of the present study she had had no diuretics for 10 days and her weight had been increasing by about 0·2 kg. daily since an abdominal paracentesis 14 days previously. Her blood-urea level was 100 mg. per 100 ml.

Case 4.—*Chronic congestive cardiac failure.* This man, aged 57, developed cardiac failure in June, 1955. Treatment with twice-weekly injections of mersalyl and dietary salt restriction proved inadequate. When the study was started he had not had any injections for 6 days, and he was gaining weight at a rate of about 0.23 kg. per day. The blood-urea level was 33 mg. per 100 ml.

Case 5.—*Portal cirrhosis of the liver.* This man, aged 67, developed generalised œdema and ascites in March, 1957. The liver was hard and greatly enlarged. His serum-albumin level was 2·0 g. per 100 ml. and flocculation tests of liver function were grossly abnormal. In the 13 days before the present study he was on a diet containing 15 mEq. of sodium per day, and he was losing weight at a rate of about 0·2 kg. daily. The blood-urea was 37 mg. per 100 ml.

Results in Animals

In dog J aldosterone produced a sharp fall in the rate of sodium excretion and a rise in the rate of potassium excretion (fig. 1). This effect was partially inhibited by the spirolactone (solution). The values obtained when SC 8109 was given alone do not differ significantly from the control. In M spirolactone (microcrystalline suspension) given by itself reduced sodium excretion considerably (table I). The response to aldosterone with spirolactone changed with time; initially there was marked inhibition of sodium retention, but after 3 months this did not occur.

TABLE I—EFFECT OF INTRAMUSCULAR ALDOSTERONE AND SPIROLACTONE (SC 8109), ALONE AND TOGETHER, ON URINARY EXCRETION OF SODIUM AND POTASSIUM (ADRENALECTOMISED DOG M)

—	Date (1958)	Urinary excretion (mEq./6 hr.)	
		Sodium	Potassium
Control	April 30	49	8
	July 30	49	10
dl-Aldosterone (500 μg.) ..	June 11	21	14
SC 8109 (100 mg.)	June 4	18	7
Aldosterone + SC 8109 ..	May 15	57	12
	July 7	36	11
	Aug. 6	20	12

Physiological saline (140 ml.) and water (70 ml.) were given by stomach-tube at 0, 2, and 4 hr. Total 64 mEq. sodium.

Results in Man

Nephrotic syndrome.—Case 1 was given a 6-day course of intramuscular SC 8109 (microcrystalline suspension) in April, 1958, and the results are shown in fig. 2 and table II.

During the study the plasma-sodium concentration fell from 140 to 135 mEq. per litre and plasma-chloride rose from 97 to 104. There was initial potassium retention with rise of the plasma-level from 3·3 to 4·4 mEq. per litre. The increase of urinary potassium on the last 2 days of treatment was associated with fever and an upper respiratory tract infection. The fæcal sodium/potassium ratio was 0·32 in the control period, 0·42 and 0·63 in the two treatment periods, and 0·48 in the 3 days after spirolactone administration. Urinary 17-hydroxy-corticosteroids and 17-ketosteroids did not show any significant change.

Case 2 was given spirolactone (microcrystalline suspension) by mouth; by this route it is said to be one-fifth as effective as by intramuscular injection. The response is shown in fig. 3. The aldosterone secretion-rate was 353 μg. per 24 hours before spirolactone, and 695 μg. per 24 hours on the 6th day.

Congestive cardiac failure.—Case 3 was treated with spirolactone solution given intramuscularly. Spirolactone by itself produced a small increase of urinary sodium excretion (from 1–2 mEq. to 26 mEq. per 24 hours) (fig. 4). Chlorothiazide increased the urinary output of potassium

TABLE II—EFFECT OF A 6-DAY COURSE OF SC 8109 ON ELECTROLYTE BALANCE IN CASE 1

Period	Balance figures (mEq.)		
	Sodium	Chloride	Potassium
3 days before course	+ 11	+ 16	−30
Day 1–3 of course	−289	− 83	+41
Day 4–6 of course	−391	−315	−78
Day 1–3 after course	−256	−213	−77
Day 4–5 after course	− 19	− 21	+ 3

and chloride and to a smaller extent that of sodium. When spirolactone was given with the chlorothiazide there was a dramatic change with increase of urinary sodium and reduction of potassium. Finally, the effects of chlorothiazide with mersalyl and chlorothiazide with spirolactone were compared. The increases of sodium output were comparable, but the effects on potassium excretion were notably different. The alterations in plasma-electrolytes (fig. 5) are in keeping with the composition of the urine, and the reciprocal changes of blood-urea and plasma-potassium are of interest. Urinary pH 1-extractable aldosterone was 148 μg. per 24 hours on the day before spirolactone was given, and it fell to 86 μg. on the 2nd day of treatment with spirolactone alone.

A poor response to spirolactone was obtained in case 4. On the last day of a 3-day course (450 mg. per day of the solution intramuscularly) the sodium excretion was 9 mEq. per day, compared with 1 mEq. per day in the control period. Despite the disappointing increase of sodium excretion, the urinary pH 1-extractable aldosterone fell from 48 μg. on the control day to 38, 28, and 10 μg. on the 3 days of treatment.

Cirrhosis of the liver.—Case 5 responded well to a 7-day course of intramuscular spirolactone solution. His urine-sodium output rose from 26 mEq. per day (mean of 10 control days) to 216 mEq. per day on the 4th day of treatment. The electrolyte balance and changes in body-weight are shown in table III.

Over a period of 8 days he lost 7·7 kg. body-weight, 999 mEq.

sodium, and 850 mEq. chloride. There was no loss of potassium, neither was there any change of plasma-electrolyte concentrations. The fæcal sodium/potassium ratio was 0·16 in the control period (9 days) and 0·26 in the treatment period (7 days).

Aldosterone secretion-rates were 188 μg. per 24 hours before treatment and 205 μg. per 24 hours on the last day of spirolactone. Corresponding figures for pH 1-extractable urinary aldosterone were 8·4 and 11·8 μg. per 24 hours.

Discussion

Our studies with adrenalectomised dogs confirm that the spirolactone SC 8109 inhibits the sodium retention and potassium loss induced by aldosterone, and that it does not increase urinary sodium excretion when given by itself. In normal men SC 8109 will antagonise the effects of aldosterone not only on sodium and potassium excretion (Ross and Bethune 1959) but also on urinary ammonia output and titratable acidity (Liddle 1958). The dose of SC 8109 needed is of the order of 1000 times the amount of aldosterone given. In Addison's disease Liddle has shown that the compound can only induce sodium loss while deoxycortone is being given. Normal subjects whose aldosterone output has been suppressed by a high-sodium diet will not respond; but, when aldosterone production is stimulated by salt restriction, SC 8109 increases urinary sodium excretion. In a patient with an aldosterone-secreting tumour of the adrenal gland, Salassa and his colleagues (1958) observed sodium loss and slight potassium retention in response to SC 8109 before operation when urine-aldosterone excretion was high. After removal of the tumour aldosterone excretion was very low, and the spirolactone was ineffective. These findings seem to establish that the spirolactones act by antagonising the peripheral effects of aldosterone; and it might be expected that the clinical response in patients with œdema would be related to the amount of aldosterone being secreted by the adrenal glands.

Aldosterone estimations were made on four of the patients in this study. In two the actual secretion-rates were measured, and in the other two urinary pH 1-extractable aldosterone. There was little correlation between the aldosterone levels and response to spirolactone. Normal subjects on unrestricted diets have aldosterone secretion-rates of 70–315 μg. per 24 hours (Ulick et al. 1958, Jones et al. 1959). With salt restriction these workers have reported rates of 780 and 930 μg. per 24 hours. The secretion-rates in case 2 (nephrotic syndrome) and case 5 (cirrhosis) on low-sodium diets were 353 and 188 μg. per day. When these measurements were made the patients were losing weight and the urinary sodium excretion exceeded the intake. Despite the low secretion-rates there was a definite response to spirolactone, and case 5 lost 1000 mEq. of sodium and became œdema free following a 7-day course. In contrast to this the two patients with cardiac failure had evidence of increased aldosterone production. The urinary pH 1-extractable aldosterone was 148 μg. per 24 hours in

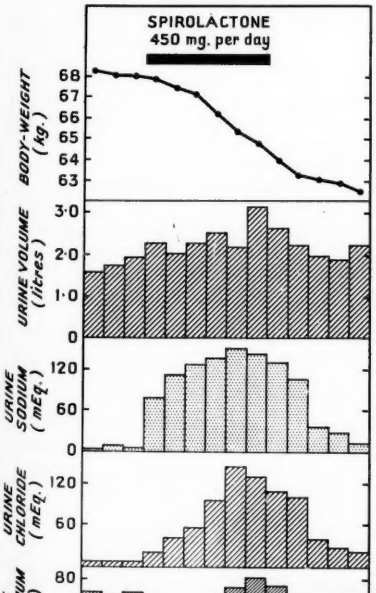

Fig. 2—Case 1 (nephrotic syndrome). Effect of 6-day course of spirolactone on body-weight, urine-volume, and electrolytes.

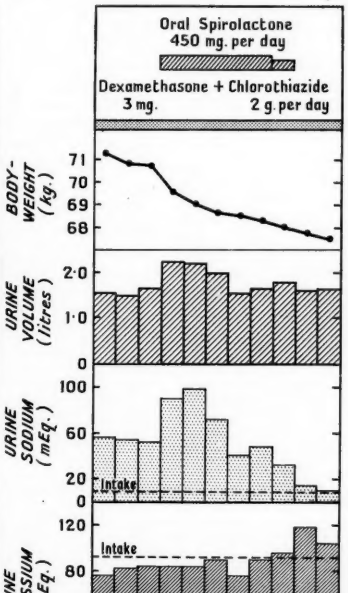

Fig. 3—Case 2 (nephrotic syndrome). Effect of 6-day course of oral spirolactone on body-weight, urine-volume, and electrolytes.

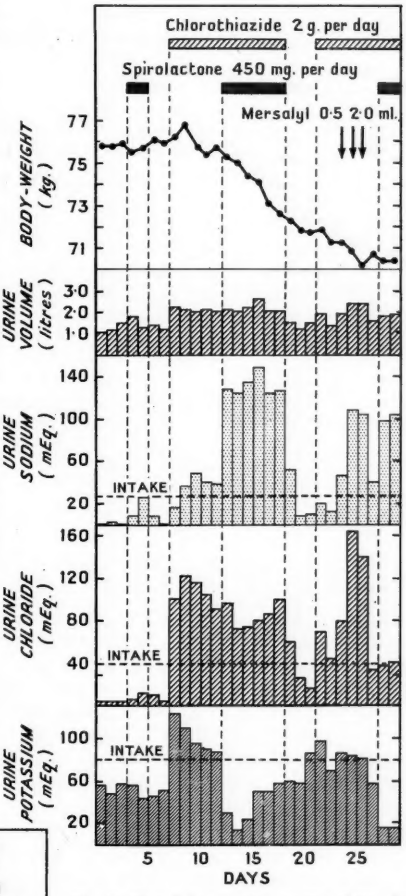

Fig. 4—Case 3 (congestive cardiac failure). Effect of spirolactone, mersalyl, and chlorothiazide on body-weight, urine-volume, and electrolytes.

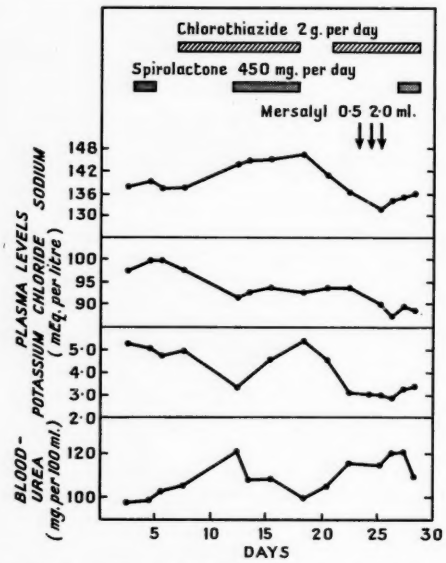

Fig. 5—Case 3. Changes of plasma-electrolyte concentration and blood-urea.

case 3, and 48 μg. in case 4, compared to the normal range of 4·6–23·5 (Ayres et al. 1957). In both these patients the response to spirolactone was disappointing. This could have been because too little spirolactone was given, but the aldosterone excretion in case 4 fell to normal by the end of the 3-day course and there was still little response. From these preliminary observations it seems likely that aldosterone is only one of the factors involved in œdema formation in these conditions, and that if the action of a normal amount of circulating aldosterone is inhibited a satisfactory diuresis may be produced.

A further unexpected finding in this study is the fall in urinary aldosterone excretion in the two cases of cardiac failure while they were receiving spirolactone. Successful treatment of this condition by the usual methods is associated with a fall of urinary aldosterone excretion (Duncan et al. 1956, Wolff et al. 1958), but in cases 3 and 4 the fall occurred without any diuresis. Liddle (1958) and Bolte et al. (1958) measured the aldosterone excretion when patients were being treated with spirolactone, and found that, when the sodium output increased, aldosterone excretion either went up or remained unchanged. Cases 2 and 5 behaved in this manner. Thus, among other things, our findings in cases 3 and 4 are compatible with inhibition of the hypothalamic aldosterone controlling centre by spirolactone. This implies the possible existence of a "feedback" mechanism in the regulation of aldosterone secretion.

There have been few reports of the use of spirolactones in the treatment of patients with œdema.

Liddle (1957, 1958) observed increased sodium excretion in seven patients with cardiac failure or the nephrotic syndrome. Bolte et al. (1958) reported a good diuresis in two patients with cirrhosis given SC 8109 by mouth; Kerr et al. (1958) and Morrison and Chalmers (1958) had less satisfactory results, but they were using intramuscular injections of the microcrystalline suspension. Our results with dog M show that with time the microcrystalline suspension given by intramuscular injection loses its effect.

TABLE III—EFFECT OF A 7-DAY COURSE OF SC 8109 ON ELECTROLYTE BALANCE IN CASE 5

Period	Change in body-weight (kg.)	Balance figures (mEq.)		
		Sodium	Chloride	Potassium
3 days before course..	−0·75	− 34	− 40	+13
Day 1–3 of course ..	−2·35	−353	−224	+29
Day 4–7 of course ..	−4·35	−543	−523	− 2
Day 1–3 after course	−1·35	−137	−156	− 3
Day 4–5 after course	0	+ 15	− 8	+29

Thus spirolactone (SC 8109), used alone or in conjunction with other diuretics, may have a place in the management of patients with severe fluid retention. It has the advantage that sodium and chloride are lost in physiological proportions, and that potassium excretion is unchanged or may actually fall. In one case of cardiac failure (case 3) the addition of SC 8109 to chlorothiazide therapy greatly increased sodium excretion and reversed a negative potassium balance.

Summary

The effect of a steroidal spirolactone (SC 8109) on sodium, chloride, and potassium metabolism was studied in two adrenalectomised dogs and in five patients with œdema.

In the adrenalectomised dogs SC 8109 inhibited the renal effects of aldosterone.

In two patients with the nephrotic syndrome and one with cirrhosis of the liver associated with severe fluid retention a satisfactory diuresis was obtained, with sodium loss and potassium retention. Two patients with cardiac failure showed little response to SC 8109 alone, but in one of them a good diuresis resulted when it was combined with chlorothiazide. Sodium and chloride were lost in physiological proportions.

There was little relation between the response to SC 8109 and either the aldosterone secretion-rate or the urinary excretion of pH-1-extractable aldosterone.

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MATERNAL INFLUENZA AND CONGENITAL DEFORMITIES

A PROSPECTIVE STUDY

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IN an investigation into the incidence of congenital deformities in Dublin (Coffey and Jessop 1955) it was noted that 18·4% of the mothers of abnormal babies gave a history of having had what they termed "influenza" during their pregnancy and that the majority of these had had the illness during the first trimester. Since there was no epidemiological or laboratory evidence to confirm the patient's report of the diagnosis, its precise significance could not be established. However, when it was predicted that the pandemic of Asian influenza would probably reach Ireland in October–November, 1957, it was decided to use this opportunity to investigate further the possible relation of maternal influenza to fœtal deformities. The fact that the onset of the epidemic could be foreseen enabled the plans for this study to be prepared in advance.

Method

The investigation was carried out in the three Dublin maternity hospitals used in the 1955 survey; these hospitals cater for 80% of the city's births. It covered the period Oct. 1, 1957, to Oct. 1, 1958. During the period Oct. 1, 1957, to June 1, 1958, all women who attended the antenatal clinics of these three hospitals were asked "Have you had influenza during this pregnancy?" For convenience a special stamp was prepared by which an imprint of this question was made on the case-record sheet. The patient's answer was recorded, and where appropriate the date of the attack. For each woman who had had influenza another who attended the antenatal clinic on the same day at about the same stage of pregnancy, but who had not been infected, was taken as a control. When each of these women came to be delivered the condition of the baby was recorded. Subsequent analysis showed that the maternal-influenza and control groups resembled each other closely in their distribution in relation to age, to parity, and to ABO and Rh blood-groups.

As in the 1955 survey, only major anomalies easily diagnosed at birth were noted. It is hoped to examine the cases again later, to identify abnormalities not apparent at birth.

Results

In the eight months during which patients were being interrogated, 669 reported that they had had influenza. 2 of these were later found not to be pregnant and we were unable to trace 4 others; so 663 cases were available for analysis. 8 mothers who had had influenza gave birth to twins, making a total of 671 babies in this group. 1 mother in the control group had triplets and 7 had twins; so the total number of babies in this group was 672. 1 twin in the control group was a papyraceous fœtus, and there were two miscarriages among the mothers who had had influenza and three among the controls. For the purpose of this analysis these were not regarded as deformities.

No maternal death occurred in the control group. 1 mother, a primipara who had had influenza about the sixteenth week of her pregnancy, died at term of post-partum hæmorrhage. Her infant was later found to have a cerebral tumour.

There was 1 case of cerebral palsy amongst the babies born to women who had had influenza but it was not included in the list of congenital defects.

The distribution of mothers who had had influenza during pregnancy and controls is shown in table I in relation to the three hospitals and to the incidence of malformations. The overall incidence in the control group is very close to that obtained in the earlier survey (Coffey and Jessop 1955). On the other hand, in the control group the distribution of abnormalities between the three hospitals is quite different from that noted previously—a difference which may be accounted for by the smallness of the sample at present being analysed (663 cases, compared with 12,552 in 1955).

The incidence of malformations in the offspring of the total sample of mothers who had had influenza is more than double that in the controls. This is significant at the 2% level. The close similarity of distribution in relation to age and parity between the mothers who had had influenza and the controls mentioned above makes it unlikely that either of these factors could have contributed to this result.

TABLE I—INCIDENCE OF CONGENITAL DEFORMITIES IN OFFSPRING OF MOTHERS WHO HAD HAD INFLUENZA DURING PREGNANCY AND OF CONTROLS

—	Rotunda	National maternity	Coombe	Total
Mothers who had influenza:				
Normal births	214	295	130	639
Malformed births	6	12	6	24
Total	220	307	136	663
Malformed births as % of total	2·7	3·9	4·4	3·6
Controls:				
Normal births	214	304	135	653
Malformed births	6	3	1	10
Total	220	307	136	663
Malformed births as % of total	2·7	1·0	0·7	1·5
Previous survey (Coffey and Jessop 1955):				
Malformed births as % of total	1·41	1·86	1·57	1·63

The distribution of the various abnormalities (table II) shows that they were almost entirely of the central nervous system and that anencephaly was commoner than any other. The proportion of anencephaly to other abnormalities among the children of mothers who had had influenza is very similar to that in the controls and is also very close to the proportion (29·5%) found in our earlier survey. For the sake of simplicity, when constructing table II, cases of multiple defect were entered only under the defect which was regarded as the most serious. Thus when anencephaly and spina bifida occurred together only the former was included in the table.

Tables III and IV were constructed with a view to finding out if the period of pregnancy at which the attack

TABLE II—DISTRIBUTION OF ABNORMALITIES

—	Rotunda		National maternity		Coombe		Total	
	Cases	Con-trols	Cases	Con-trols	Cases	Con-trols	Cases	Con-trols
Anencephaly	3	2	5	1	2	0	10	3
Spina bifida	1	1	1	0	2	0	4	1
Meningocœle and encephalocœle	1	0	1	1	1	0	3	1
Hydrocephaly	1	1	0	0	0	1	1	2
Mongolism	0	0	2	0	0	0	2	0
Others	0	2	3	1	1	0	4	3
Total	6	6	12	3	6	1	24	10

TABLE III—DISTRIBUTION OF BIRTHS TO CASES IN RELATION TO HOSPITALS AND TO PERIOD OF PREGNANCY AT WHICH ATTACK OF INFLUENZA OCCURRED

Weeks	Rotunda		National maternity		Coombe		Total	
	Normal	Malformed	Normal	Malformed	Normal	Malformed	Normal	Malformed
0–4	4	2	14	1	5	0	23	3
5–8	2	0	23	1	7	0	32	1
9–12	10	0	26	3	9	1	45	4
13–16	16	0	31	3	10	0	57	3
17–20	25	0	23	1	12	1	60	2
21–24	23	0	44	3	15	1	82	4
25+	134	4	133	0	72	3	339	7
Total	214	6	294*	12	130	6	638*	24

* In 1 case the date of the influenza attack was not recorded.

of influenza occurred had any bearing on the incidence of malformations. In table III the numbers are too small for any conclusions to be drawn, but it is clear from table IV that the risk of a malformation was greatest if the illness took place in the first trimester and that it declined progressively in the two subsequent trimesters. Indeed, in the third trimester it was little higher than in the controls or in the 1955 survey. In these tables the period of pregnancy is reckoned from the date of onset of the last menstrual period.

Various workers (e.g., Böök and Rayner 1950, McMahon and McKeown 1952, Coffey and Jessop 1957, 1958) have pointed out that the incidence of stillbirths and prematurity and the ratio of females to males are higher in babies with severe defects of the nervous system than in normal babies. Since a very high proportion of the

TABLE IV—DISTRIBUTION OF BIRTHS TO CASES, ANALYSED BY TRIMESTER IN WHICH ATTACK OF INFLUENZA OCCURRED

Offspring	First trimester	Second trimester	Third trimester	Total
Normal ..	100	199	339	638*
Malformed ..	8 (7·4%)	9 (4·3%)	7 (2·0%)	24 (3·6%)
Total ..	108	208	346	662

$\chi^2 = 7{\cdot}24$ n=2 $0{\cdot}05 > P > 0{\cdot}025$

* In 1 case the date of the attack of influenza was not recorded.

abnormalities in this study were of the nervous system an analysis was undertaken to see if this was true when the deformities were associated with maternal influenza. The results are presented in table V, which shows that the incidence of stillbirths in the maternal-influenza group as a whole was almost identical with that in the controls. Although the proportion of stillbirths was high in the malformed children born both to mothers who had had influenza and to the controls, there was no significant difference between the two groups.

The incidence of prematurity in the whole maternal-influenza group was not significantly different from that in the control group, and in both it was about the usual level for the Dublin maternity hospitals. When the congenitally malformed babies were taken separately, however, the incidence of prematurity was very high in infants born both to mothers who had had influenza and to those who had not. It was, in fact, definitely higher in the former than in the latter, but it would probably be unwise to attach much importance to this difference in view of the small numbers concerned.

The sex ratio of the children, whether they were normal or abnormal, was not affected by influenza, though the malformed babies in both maternal-influenza and control groups showed the expected preponderance of females.

TABLE VI—VIRUS CHARACTERISTICS AND CONGENITAL DEFECTS

Disease	Size (mμ)	Evidence of blood transport		Congenital defects
		Clinical	Laboratory	
Rubella ..	?	+	+	++
Measles ..	circa 140	+	+	–
Chickenpox ..	220–250	+	+	–
Mumps ..	140	+	+	–
Influenza ..	100	?	–	+

Discussion

Three points of interest arise from these observations:

(1) The effect of this type of virus infection on the outcome of a pregnancy.

(2) The nature of the infection in this investigation.

(3) The means by which the embryo or fœtus was affected.

Virus Infections and Pregnancy

Since Gregg (1941) reported a high incidence of congenital abnormalities of the eye in children born to women who had had rubella during pregnancy there have been many reports on the influence of maternal virus infections of various kinds on the unborn child.

Hill et al. (1958) concluded that rubella was the only virus infection which carried a significant risk. They did not, however, make any reference to influenza. More recently, Siegel and Greenberg (1959) have reported the results of a study of virus diseases in pregnancy, but influenza did not find a place in the list of diseases studied. We have not been able to trace any mention of this infection in reports of human congenital deformities, though Adams et al. (1956) noted effects in mice inoculated with human-strain influenza just after mating.

TABLE V—BABIES BORN TO 671 CASES AND 672 CONTROLS ANALYSED BY CONDITION AT BIRTH, SEX, AND BIRTH-WEIGHT

Weight (g.)	Cases							Controls						
	Normal births			Malformed births			Total	Normal births			Malformed births			Total
	Male	Female	No rec. of sex	Male	Female	No rec. of sex		Male	Female	No rec. of sex	Male	Female	No rec. of sex	
Born alive:														
< 1250 ..	..	1	..	..	2	..	3	..	..	..	..	..	..	..
1250–1999 ..	2	2	..	..	2	..	6	4	2	..	..	1	..	7
2000–2499 ..	23	13	..	2	2	..	40	15	20	..	..	1	..	36
2500+ ..	271	260	..	4	4	..	539	289	295	..	2	2	..	588
No record ..	26	19	18	..	1	1	65	10	9	2	1	..	..	22
Total ..	322	295	18	6	11	1	653	318	326	2	3	4	..	653
Stillborn:														
<1250 ..	1	..	..	1	2	..	4	..	1	..	..	2	..	3
1250–1999 ..	..	2	..	..	1	..	3	3	..	..	..	..	..	3
2000–2499 ..	1	1	..	..	2	..	4	2	1	..	..	..	..	3
2500+ ..	2	1	..	..	..	..	3	2	3	..	..	1	..	6
No record ..	1	1	2	..	..	..	4	1	..	3	..	..	..	4
Total ..	5	5	2	1	5	..	18	8	5	3	..	3	..	19

8 sets of twins among cases; 7 sets of twins and 1 set of triplets among controls.

It appears that the incidence of malformations in our sample of children born to mothers who had influenza during pregnancy was 2·4 times that in the control group. The distribution of abnormalities was not greatly different from that in the control group, so the influence of the infection was not directed towards any specific deformity.

As with rubella the risk increases greatly when the infection is experienced early in pregnancy. In the first trimester it was over 7%. While this figure is not alarming compared with the risk sometimes claimed for rubella, and is even far short of the more conservative estimates for the latter infection, it deserves serious notice because of the frequency of epidemics of influenza, the absence of a lasting immunity following an attack, and, consequently, the high adult attack-rate during an epidemic. It strongly suggests the advisability of affording protection by vaccination to pregnant women when an epidemic is in progress or pending.

Nature of the Infection

Unfortunately it was not feasible to identify the virus in the cases in this investigation. Virus isolation was impossible because none of the patients was seen during an attack, and the lapse of time between the attack and the recording of particulars would have rendered the serological tests at our disposal at that time of doubtful value in a considerable number of the cases. On the other hand, there can be little doubt about the type of infection prevalent then in Dublin. The first cases were noted in accordance with the epidemiological forecast, and the outbreak was homogeneous. Meenan (1959) isolated virus A regularly from cases during this period and found no other virus. It is safe to assume, therefore, that those patients who replied in the affirmative to the question had indeed experienced an attack of Asian influenza.

How Can the Influenza Virus Damage the Embryo?

The most obvious explanation of the fœtal damage associated with a virus disease is that it is caused by the virus crossing the placenta, having been carried thither by the blood, and this sequence of events is tacitly assumed for rubella. On this view, before we could assess the risk to the fœtus we should know whether or not any given infection is associated with viræmia, the conditions that determine the crossing of the placenta, and the specific effect of any particular virus on the process of development.

Our knowledge on the first of these points is incomplete and of the second and third practically non-existent. We can infer that certain viruses are spread by the blood-stream from the clinical features of the diseases they cause; but in only four of those which have been investigated as potential causes of congenital defects is there laboratory evidence, direct or indirect, of blood transport: direct in the cases of measles, rubella, and mumps, in which the virus has been demonstrated in the blood; and indirect in the case of chickenpox, in which it has been grown from vesicle fluid. The conditions governing the passage across the placenta of a virus which is probably multiplying in the tissues must be very complex—certainly much more complex than those entirely physical conditions which are taken into account when the larger protein molecules, such as antibodies, are being considered. Particle size, of itself, is probably not of great importance, but since it is the only factor of which we have any knowledge it may be worth noting in passing.

Table VI summarises the information at our disposal about those viruses which have been studied in relation to congenital defects. In each of the first four there is evidence of blood transport; but in only one—rubella—do we find a maternal infection associated with congenital anomalies. In the case of influenza the position is even more difficult; for, while the virus can be readily isolated from the respiratory tract of patients, it has neither been isolated from the blood nor shown to be present there in a pathogenic form. This is probably because of the powerful inhibitory action of plasma-mucoproteins. It is not impossible that this inhibition may be reversible, and if it could be shown to be so the situation would have to be reviewed. But if it should ultimately be firmly established that the virus is not carried by the blood, at any rate in a pathogenic form, can we offer any explanation of the association, indicated in the present paper, between maternal influenza and fœtal damage?

It has been shown experimentally by many workers (e.g., Ingalls et al. 1950, Millen et al. 1954) that the embryo can be damaged by various chemical agents, some of which are even normal metabolites. In an attack of influenza there can be no lack of metabolites arising from the damaged mucosa of the respiratory tract or even from the virus itself. Such metabolites must be largely responsible for the systemic reaction which the patient experiences. Examples of damage to organs remote from the respiratory tract have been reported in connection with the epidemic of Asian influenza (Bourne and Wedgwood 1959, Skanse and Miörner 1959). It is reasonable to suppose that chemical substances, such as those which provoke these reactions, could cross the placenta and interfere with the development of the embryo. Consequently, the absence of proof that the influenza virus invades the blood-stream does not, in our opinion, conflict with the results now reported; nor would these results necessarily be invalidated if it is eventually proved that blood from a case of influenza definitely does not contain the virus.

Summary

During the 1957–58 epidemic of Asian influenza in Dublin 663 pregnant women attending antenatal clinics in the three maternity hospitals stated that they had had influenza during their pregnancy. The incidence of congenital deformities in the children born to these women was 2·4 times that in the children of the control group. This is a significant increase.

The abnormalities were almost entirely of the central nervous system, and the commonest was anencephaly.

The proportion of anencephaly to other abnormalities was the same in the children of the maternal-influenza group as in the children of the controls.

The risk of a malformation was greatest if the infection took place in the first three months, and it declined progressively in the two subsequent trimesters.

There was no significant difference in the incidence of stillbirths and prematurity between the maternal-influenza group and the controls, and the sex ratio of the children was the same in the two groups.

We wish to acknowledge our indebtedness to the Masters of the three Dublin maternity hospitals and their staffs in the outpatients' and medical records departments; without their ready cooperation this work could not have been done. Our colleagues, Dr. Roy M. Acheson, lecturer in social medicine, and Mr. E. H. Thornton, lecturer in statistics, gave us valuable assistance, the former by helping to plan the early stages of the study and the latter by analysing the results. Our thanks are also due to Mrs. E. MacSweeney and Miss M. Hanna for help in the preparation of the tables and the typescript.

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PEPTIC ULCERATION AND ENDOCRINE DISEASE IN NECROPSY MATERIAL

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THE occurrence of peptic ulceration in patients with endocrine disease has been known for a long time. It was not, however, until Zollinger and Ellison (1955) described their syndrome of non-insulin-secreting islet-cell adenoma, gastric hypersecretion, and atypical peptic ulceration which failed to respond to the usual medical and surgical remedies, that the relationship between endocrine disease and peptic ulceration attracted much attention. The literature on this problem has been reviewed in this journal, and the question was posed: "Is peptic ulcer due to endocrine disease?" (*Lancet* 1959). To find the prevalence of endocrine disease associated with peptic ulceration, we reviewed all cases showing such a lesion at necropsy in which one or more of the endocrine glands were examined. As a control series, consecutive adult cases, free from gastrointestinal lesions, were collected from the necropsy files. In both series the number of males and females were the same.

TABLE I—ENDOCRINE DISEASE IN 426 NECROPSY CASES WITH PEPTIC ULCERS

Endocrine glands	No. of cases examined	No. with neoplasms	No. with hyperplasia	Total with lesions
Pituitary ..	224	15	0	15 (6·7%)
Parathyroid ..	70	4	8	12 (17·1%)
Thyroid ..	392	15	28	43 (10·9%)
Pancreas ..	419	3	0	3 (0·7%)
Adrenal ..	417	18	6	24 (5·7%)

Results

There were 426 cases. Table I shows the number of cases in which individual endocrine glands were examined with the number and types of lesions found. By expressing the number of involved endocrine glands as a percentage of the total examined, the prevalence of peptic ulcer cases with coexistent endocrine disease was obtained. To avoid repetition it can be said at this point that the same regime was adhered to when drawing up all the other tables.

The pancreas, the adrenals, and the thyroid glands were examined in 98–92%, the pituitary in 52%, and the parathyroids in 16% of cases.

Peptic ulceration was, however, more commonly associated with lesions in the parathyroid and the thyroid glands (17·1% and 10·9% cases respectively), less commonly associated with lesions in the pituitary and the adrenal glands (6·7% and 5·7% respectively), while in only 3 cases (0·7%) of peptic ulcer were the lesions noted in the pancreatic islets.

In 1 of these 3 cases, a male, the pancreatic islet-cell adenoma was the only endocrine lesion found. The 2nd, also a male, showed a pancreatic islet-cell adenoma, and hyperplasia of the adrenal cortex and the parathyroid glands. The 3rd case, a female, had an α-cell tumour of the pancreatic islets, which was malignant and had metastases in the regional lymph-nodes, liver, lungs, and heart, associated with hyperplasia of the adrenal cortex and eosinophil adenomata of the parathyroid glands (to be published separately).

Influence of Endocrine Disease on Site of Ulcer

There were 210 cases with gastric ulcers and 216 cases with duodenal ulcers.

It is seen from table II that there is no significant difference between the percentage of cases showing lesions in the pituitary and the adrenal glands, irrespective of the site of the ulcer. However, the parathyroid glands were five times and the thyroid glands were twice as often involved in cases with duodenal ulcer as in cases with gastric ulcer. The islets of the pancreas were involved in 2 cases with gastric ulcer and in 1 case with duodenal ulcer.

TABLE II—INFLUENCE OF ENDOCRINE DISEASE ON SITE OF ULCER

Site of ulcer	Endocrine gland	No. examined	Neo-plasia	Hyper-plasia	Total
Stomach ..	Pituitary	96	7	0	7 (7·6%)
	Parathyroid	34	1	1	2 (5·6%)
	Thyroid	191	7	9	16 (8·4%)
	Pancreas	218	2	0	2 (0·9%)
	Adrenal	193	11	2	13 (6·7%)
Duodenum	Pituitary	128	8	0	8 (6·3%)
	Parathyroid	36	3	7	10 (27·7%)
	Thyroid	201	8	19	27 (13·4%)
	Pancreas	201	1	0	1 (0·5%)
	Adrenal	224	7	4	11 (4·9%)

Endocrine Disease and Peptic Ulceration Related to Sex

Females accounted for 110 cases and males for 316 cases. Changes were found twice as often in the pituitary gland (table III) and three times as often in the parathyroid glands in males, while the pancreas, the adrenals, and the thyroid glands were involved in a higher percentage of cases in females.

Endocrine Disease in Control Series of Necropsy Cases

There were 426 cases, 110 of which were females and 316 males (vide supra). The findings are set out in table IV. The pancreas and the adrenal glands were each examined in 97%, the thyroid gland in 93%, the pituitary gland in 91%, and the parathyroid glands in 18% of cases. The percentage of cases showing some change in the individual

TABLE III—ENDOCRINE DISEASE AND PEPTIC ULCERATION IN FEMALES AND MALES

Sex	Endocrine gland	No. examined	Neo-plasia	Hyper-plasia	Total
Female ..	Pituitary	70	3	0	3 (4·3%)
	Parathyroid	26	1	1	2 (7·7%)
	Thyroid	108	11	16	27 (25%)
	Pancreas	111	1	0	1 (0·9%)
	Adrenal	107	7	4	11 (11·2%)
Male ..	Pituitary	154	12	0	12 (7·8%)
	Parathyroid	44	3	7	10 (22·7%)
	Thyroid	284	4	12	16 (5·6%)
	Pancreas	308	2	0	2 (0·6%)
	Adrenal	310	11	2	13 (4·2%)

TABLE IV—ENDOCRINE DISEASE IN 426 CONTROL NECROPSY CASES

Endocrine gland	No. examined	Neoplasia	Hyperplasia	Total
Pituitary ..	390	21	0	21 (5·4%)
Parathyroid ..	76	6	7	13 (17·1%)
Thyroid ..	395	11	18	29 (7·4%)
Pancreas ..	414	0	0	0
Adrenal ..	412	4	1	5 (1·2%)

endocrine glands is shown in table IV. In no case was any change seen in the islets of the pancreas.

Discussion

The results of this investigation would not support the idea that the parathyroid glands play any significant role in the ætiology of peptic ulceration. These glands are, nevertheless, more frequently involved in males and in duodenal-ulcer patients. The exact significance of this is not understood. However, Haynes (1957) at the Mayo Clinic found that 24% of patients with hyperparathyroidism had a peptic ulcer and in addition 15–20% of patients had gastrointestinal symptoms, although ulceration was not determined. Fisher and Flandreau (1957) also believe that increased parathyroid secretion may play a significant role in the ætiology of peptic ulceration.

Morphological changes were encountered slightly more frequently in the pituitary and the thyroid glands of peptic-ulcer patients than in those free from intestinal lesions, but the difference is small and does not appear to be statistically significant.

No changes were found in the islets of the pancreas in the cases forming the control series, but lesions were encountered on three occasions in patients with a peptic ulcer. The part played by a pancreatic islet-cell tumour in the ætiology of peptic ulceration has won much attention since Zollinger and Ellison (1955) and Ellison (1956) published their observations. They suggested that glucagon as secreted by the α cell might represent the ulcerogenic factor. However, the results obtained by Poth and Fromm (1950) and Eiseman (1956) following the administration of glucagon to dogs do not support this hypothesis, although Poth (1955) observed an increase in gastric secretion by adrenocortical hyperactivity shown by a rise in urinary 17-hydroxycorticosteroids following the use of glucagon in the same species.

This observation is supported by the findings in this review, in that the adrenal glands, although showing changes in only a small percentage of cases in both series, were five times more commonly involved in patients with a peptic ulcer. That hyperactivity of the adrenal glands can cause peptic ulceration is not unknown; and this hyperactivity is indicated by the formation of ulcers following prolonged periods of emotional stress.

The occurrence of gastric hypersecretion and peptic ulceration in Cushing's syndrome (Kyle et al. 1956, Swan and Stephenson 1935), and also following steroid therapy (Sandweiss 1954, Bollet et al. 1955), is evidence in support of this hypothesis. On the other hand the ulcer and the adrenal hyperplasia may well have a common ætiology.

The site of the ulcer would not appear to be influenced by lesions in the pituitary or the adrenal glands. On the other hand the parathyroid and the thyroid glands show changes in a higher percentage of cases with a duodenal ulcer.

Finally the pituitary and the parathyroids are more commonly involved in male patients with a peptic ulcer, while changes in the thyroid and the adrenal glands are found more often in female patients.

In both instances no conclusions can be drawn regarding the pancreas, since the series is too small.

Summary

Endocrine disease in 426 cases with peptic ulceration and 426 control cases is reported.

Tumours of the pituitary, parathyroid, and thyroid glands would appear to have no specific association with peptic ulceration.

There is some evidence that the adrenal glands and possibly the pancreas may influence peptic ulceration in some way.

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ORALLY INDUCED POSITIVE NITROGEN BALANCE AND THE TOTAL EXCHANGEABLE ALBUMIN POOL

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A RELATION between gain or loss in total body protein and in circulating plasma-albumin was first described by Sachar et al. (1942). Their estimate of total circulating albumin involved an assumed blood-volume equivalent to $^1/_{20}$ body-weight. Sterling (1951), using albumin labelled with radioactive iodine (^{131}I-albumin), introduced the concept of the total exchangeable albumin pool, which contains an amount of albumin somewhat greater than twice that in the circulating blood.

Since then much work has been devoted to this pool, and mathematical objections have been raised to Sterling's original method of measuring it. The equilibrium-time method of Campbell et al. (1956) is convenient for determining pool masses, and overcomes these objections. Another disadvantage of earlier work with ^{131}I-albumin was its partial denaturation during isolation or iodination. Iodinated plasma-proteins which are metabolically identical with biosynthetically labelled products are now available, largely through the work of McFarlane (1956) and his co-workers.

Protein nutrition in the preoperative patient is so vital that it seems desirable to test by these newer techniques the efficacy of the widely used method of preparing patients for operation by intensive high-calorie, high-protein feeding. Many workers speak in terms of positive nitrogen balance, but there is little if any proof that the desired end-result—namely, a net increase in body protein—can be obtained. The total exchangeable albumin, however, can be directly measured. In this study the albumin-pool masses of three hypoproteinæmic patients were determined before and after an intensive "protein build-up," and correlated with nitrogen balance.

Methods

Three patients with carcinoma were selected for study. Cases 1 and 2 had upper gastrointestinal malignant disease, and they were severely cachectic. Case 3 had car-

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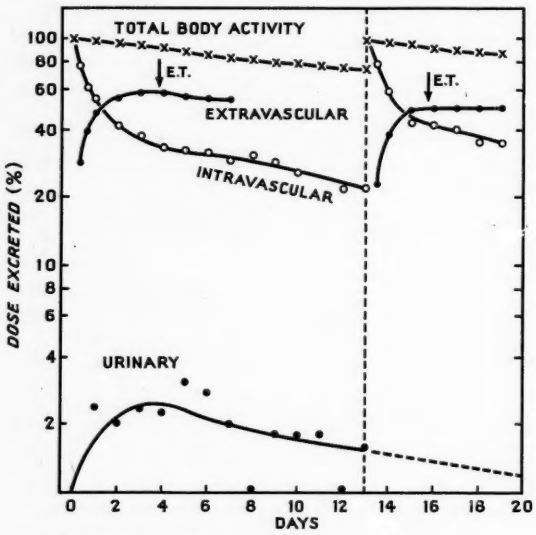

Albumin-pool studies in case 3 (for explanation see text).

cinomatosis (4 years after radical mastectomy), and had moderate recent weight loss.

Human albumin, separated on a carboxymethyl-cellulose column and iodinated by the method of McFarlane (1958), was injected into the antecubital vein of each patient. A 10-minute blood sample was used to determine plasma-volume, corrected by 3% for early loss of radioactive label. Periodic blood samples were then assayed for radioactivity and protein. Total serum-protein was determined by the Biuret method, and the albumin fraction by paper electrophoresis. The average value for all samples in each equilibration period was used. 24-hour urine and 3-day stool specimens were collected and assayed for nitrogen by the Kjeldahl procedure. Random urine samples were tested for protein by sulphosalicylic acid. Stools were tested for blood by benzidine dihydrochloride. Urine and plasma were assayed for radioactivity in the well-scintillation counter. The thyroid gland was blocked with Lugol's iodine solution in each case.

Each patient was given an initial dose of ^{131}I-albumin, and maintained for 4 days as nearly as possible in nitrogen equilibrium. In this period the initial size of the pool was determined. The patient was then given a semiliquid high-calorie, high-protein diet which produced a strongly positive nitrogen balance. After 7 days on this regime a second dose of ^{131}I-albumin, four to five times as large as the first, was given, and the size of the pool was determined again. Correction for the residual activity of the original dose was made by subtracting the extrapolated values from the plasma and urinary curves of that dose.

Results

The figure shows the curves obtained in case 3 by the equilibrium-time method.

The second dose of ^{131}I-albumin is indicated by the vertical dotted line. The percentage of the dose excreted is calculated from the daily urinary counts and volumes. The curve for total body activity is obtained by subtracting this value cumulatively from the initial value of 100%. Intravascular activity is obtained directly from the plasma-counts and plasma-volume. As the ^{131}I-albumin leaves the blood and passes into the extravascular pool the intravascular activity falls rapidly; when this curve is subtracted from the total body curve, the curve for extravascular activity is obtained. At the maximum of the extravascular curves the intravascular and extravascular pools are in transient equilibrium (E.T.), and their masses are proportional to their respective activities. Since the intravascular albumin mass is known from the plasma-albumin and plasma-volume, the total pool can be calculated.

The main findings are summarised in table I. Under the conditions employed there was no improvement in the serum-albumin level. A heavy net positive nitrogen balance was achieved in each patient without significant change in the size of the pool or in the amount of exchangeable albumin per kg. body-weight. There is a general inverse relation between the size of the pool and the daily turnover-rate of albumin but great variation exists in the absolute values (table II).

Discussion

The correction of hypoproteinæmia before surgery in the cancer-patient is of major importance. But the protein level may not have great significance unless considered with hæmodilution, blood-volume, and the size of the extravascular reserve. Direct measurement of the total exchangeable albumin, which can now be accurately accomplished, appears to give more complete information. Measurement of lean-muscle mass—a more inclusive figure—is obtainable only indirectly, but it probably varies with the circulating protein mass. My findings show that a net increase in the total exchangeable albumin cannot be achieved quickly enough by mouth when there are urgent indications for surgery.

TABLE II—RATE OF DAILY TURNOVER OF ALBUMIN DURING PERIOD OF "PROTEIN BUILD-UP"*

Case no.	Body-weight (kg.)	Albumin (g. per day)	Albumin (g. per kg. body-weight)
1	53·2	21·9	0·410
2	38·6	24·0	0·620
3	57·3	13·5	0·236

* Derived from the initial size of the pool and albumin half-life.

Two patients (cases 1 and 2) had high rates of protein synthesis despite hypoproteinæmia. Schwartz and Jarman (1959) believe that, if external loss can be ruled out, this indicates internal loss. Neither of these patients had proteinuria nor chemical melæna. It would be interesting to speculate on the possibility of internal protein shunts in patients with malignant disease.

Freeman and Matthews (1958) have examined the assumptions on which depend the validity of the calculation of pool masses. One assumption is that for any

TABLE I—RESULTS OF ORALLY INDUCED POSITIVE NITROGEN BALANCE IN THREE HYPOPROTEINÆMIC PATIENTS

Case no.	Albumin level (g. per 100 ml.*)		Equilibrium time (days)		Positive protein balance (g.)†	Size of albumin pool (g.)			Total exchangeable albumin (g. per kg. body-weight)		Half-life (days)‡
	Before treatment	After treatment	Initial	Second		Initial	Second	Change	Initial	Second	
1	2·11	2·12	2·7	3·3	371	121·4	130·6	+9·2	2·28	2·46	5·3
2	2·25	1·89	2·7	3·4	259	197·5	197·0	−0·5	5·11	4·76	8·2
3	3·52	3·25	3·8	2·7	280	215·7	209·2	−6·5	3·72	3·65	16·0

* Average level for all samples during equilibrium period.
† Nitrogen balance between the two equilibrium times multiplied by 6·25.
‡ During period of "protein build-up".

patient the pool mass and catabolic rate are constant, and most workers have assumed tacitly that they are. My findings support this assumption since, even in a state of strongly positive nitrogen balance, there was no change in the size of the pool within 7 days. I feel justified in using the equilibrium-time method because these patients were held very nearly in protein balance during the equilibration periods.

I have shown (Madden 1957) that the turnover-rate of albumin in the dog is influenced by the amount of protein in the diet. Pool sizes were not measured in this study, but since they seem to remain constant (at least in the cachectic patient) there are strong grounds for concluding that albumin synthesis varies directly with the amount of protein in the diet.

Summary

The total exchangeable albumin pool was measured in three hypoproteinæmic patients before and after a period on an intensive high-calorie, high-protein diet. In none was there a significant change in the size of the pool. Two of these patients had unusually high rates of albumin turnover despite hypoproteinæmia, unchanged pool size, and lack of evidence for external protein loss.

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CLINICAL STUDIES WITH DF^{32}P ON THE LIFESPAN OF PLATELETS

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BEFORE radioisotopes became available various methods had been devised for estimating the lifespan of platelets, but these did not yield consistent results.

In animals this was done by observing the rate of regeneration of platelets after the induction of thrombocytopenia, or by observing their rate of disappearance from the circulation, or their survival on transfusion, after heavy X-irradiation. In patients with spontaneous thrombocytopenia, with virtually no circulating platelets, survival-times were determined by transfusing with blood or platelet concentrates from normal or polycythæmic donors.

Radioisotopes provided new techniques for studying platelet lifespans. Various isotopes have been employed, the platelets being labelled either in vitro or in vivo. Most attempts at in-vitro labelling have been unsuccessful, mainly because the platelets became damaged. But recently, with improved techniques, values similar to those obtained with in-vivo labelling have been reported (Aas and Gardner 1958).

In-vivo labelling has the advantage that manipulation of the platelets is minimal. The survival of platelets thus labelled can be studied either directly or after transfusion into compatible recipients (Adelson et al. 1957). So far the only successful direct method of labelling human platelets is that described by Leeksma and Cohen (1955), employing isotopically labelled di-isopropylfluorophosphonate (DF^{32}P). This is based on the irreversible combination of DF^{32}P with esterases in the thrombocytes.

We here report the results of studies with DF^{32}P on the lifespan of platelets in hæmatological and other disorders, and describe the clinical and laboratory techniques employed.

Material and Methods

Labelled di-isopropylfluorophosphonate was obtained from the Radiobiological Institute, Rijswijk, Holland (through the kindness of Dr. L. M. van Putten). The specific activity was in the range of 45–200 μC per mg.

Radioactivity determinations were made in a G-M liquid counter. Corrections were applied for lost counts. Standard solutions consisted of di-isopropyl phosphate prepared by alkaline hydrolysis of samples of DF^{32}P of known activity.

Clinical procedure.—DF^{32}P, dissolved in peanut oil or physiological saline, was injected intramuscularly in a dose of 0·4–1·3 mg. Venepuncture was performed next day and repeated daily (or later at longer intervals) until the platelet radioactivity became too low to measure.

Technique of venepuncture.—Siliconised glassware was used throughout the collecting and fractionating procedures. 45–50 ml. of blood was collected through a no. 19/10 (14 S.G.) transfusion needle, attached to a 40 cm. length of polyethylene tubing, and inserted into an antecubital vein. The blood was allowed to flow, assisted by the pumping action of opening and clenching the fist, into a bottle containing 5 ml. of a solution containing 6% (w/v) dextran and 1% sodium ethylene diamine tetra-acetate in 0·9% sodium chloride. If the hæmatocrit was raised, proportionately more of this solution was used to achieve a final hæmatocrit of about 50%, and larger volumes of blood were collected.

Separation of platelets.—The blood was allowed to stand for $^1/_2$–1 hour at 0–4°C. In the presence of dextran the erythrocytes sedimented almost completely, leaving supernatant plasma rich in platelets and leucocytes. This supernatant was pipetted into 50 ml. centrifuge tubes, and centrifuged for 10 minutes at 123 *g* (800 r.p.m. in the M.S.E. "medium" centrifuge). The resulting platelet-rich supernatant was decanted off; the deposit contained the leucocytes and a few remaining erythrocytes. Differential cell-counts were performed on the supernatant, which was then recentrifuged, and the process was repeated until counts showed less than 1 leucocyte per 5000 platelets (usually two or three times sufficed), and the final centrifugation was performed at 1000 r.p.m. (190 *g*).

The final platelet suspension was mechanically mixed for 20 minutes, and the number of platelets per c.mm. was determined with standard white-cell-counting equipment, using 3·8% (w/v) sodium citrate as diluting fluid. The mean of 5–6 separate counts was taken. The volume of the suspension was accurately measured, and hence the total number of platelets was calculated. The sample was then centrifuged at 1738 *g* (3000 r.p.m.) for 45 minutes. The supernatant plasma was decanted off, and the deposit was resuspended in an equivalent volume of saline. Centrifugation and washing were repeated twice, and the final platelet deposit was dissolved in 2–3 ml. of 10*M* NaOH by heating at 100°C for 30 minutes. The solution was cooled and diluted to 10 ml. with 5*M* NaOH for liquid counting of ^{32}P.

The lifespan was deduced from a plot of di-isopropylfluorophosphonate content, expressed in microgrammes per 5×10^{12} platelets, against time, as described by Leeksma and Cohen (1955).

Case-reports

Clinical details are given for the three cases of thrombocythæmia, because the DF^{32}P studies, together with the

clinical and hæmatological response to treatment, seem to throw some light on the syndrome.

Case 5.—This man, aged 46, presented in 1950 with epistaxis. During the next 5 years he had recurrent hæmorrhagic episodes and developed a duodenal ulcer for which a gastrectomy was performed. (For full details see Hardisty and Wolff [1955].)

In December, 1956, he was admitted to the Royal Marsden Hospital having had chronic sepsis of two toes for a year and epistaxes for a few weeks. A blood-count showed: hæmoglobin (Hb) 94%, white blood-cells (W.B.C.) 12,700 per c.mm., and platelets 1,020,000 per c.mm., with abnormal morphology in 12%. The bleeding-time was 25 minutes, with no sign of stopping (Ivy).

The patient was treated with ^{32}P 5 mC intravenously. 2 months later he was asymptomatic and had a normal peripheral blood-picture. Hb 97%, W.B.C. 6400, and platelets 287,000.

He was admitted for reassessment 6 months later though still asymptomatic and at full-time work. The Hb was 98%, packed-cell volume (P.C.V.) 46%, W.B.C. 8500, and platelets 1,030,000. Platelet-survival studies with $DF^{32}P$ showed 16·5 days (normal range 8–10 days). No further ^{32}P was given in view of his excellent clinical condition.

The patient has remained symptom free for a further year, during which the platelet-count has never been higher than 650,000. He was last seen 18 months after treatment with ^{32}P, when the platelets numbered 350,000.

Case 8.—In February, 1947, this man, aged 50, started to get a left-sided hemiplegia, which progressed slowly. He was referred to a neurological centre with a tentative diagnosis of meningioma, but this was not confirmed. The Hb was 140%, and the red blood-cells (R.B.C.) 10,000,000 per c.mm. Polycythæmia vera with multiple cerebral thromboses was diagnosed. During the next 6 years treatment consisted of multiple venesections and iron. A barium-meal examination, performed because of indigestion, showed healed gastric and duodenal ulcers.

In 1954 his spleen became palpable below the costal margin, and during the next year he had a large hæmorrhage into a recent herniorrhaphy wound, a severe hæmatemesis, and a prolonged hæmorrhage from a tooth socket. The blood-count showed: Hb 91%, W.B.C. 27,000 per c.mm. (neutrophils 90%), P.C.V. 56%, and platelets 854,000 per c.mm. The serum-uric-acid was 8·9 mg. per 100 ml. Sternal marrow aspirate showed abundant megakaryocytes, and slight myeloid hyperplasia with normal erythropoiesis. The serum-proteins were normal. Platelet survival studies showed 13·5 days (above normal). The clinical picture was consistent with thrombocythæmia.

The patient was treated with ^{32}P 4 mC intravenously. During the next 6 months there was no further bleeding and the platelet-count dropped to 551,000. A thromboplastin-generation test revealed no abnormality, though there was deficient clot retraction and a slightly prolonged prothrombin-time. The bleeding-time was $4^1/_2$ minutes (Ivy), and the clotting-time $12^1/_2$ minutes.

He was again given ^{32}P 5 mC intravenously. 4 months later there was considerable clinical and hæmatological improvement. The Hb was 92%, R.B.C. 7,630,000, W.B.C. 4300, and platelets 140,000.

He was last seen $2^1/_2$ years after the first treatment with ^{32}P, when his thrombocythæmia was still well controlled.

Case 12.—In January, 1954, this man, aged 64, was admitted to hospital with anæmia. He gave a history of duodenal ulcer for 40 years, with many attacks of hæmatemesis and melæna. The Hb was 37%, and the P.C.V. 24%. He had hepatosplenomegaly, but liver biopsy was normal. Sternal marrow puncture showed much hyperplasia involving the red-cell series and the megakaryocytes, of which there was a great increase. The platelets were in large drifts. The patient was given blood-transfusions, and a gastrectomy was performed.

3 years later, after a cerebral thrombosis with residual numbness of one arm, he was admitted to the Royal Marsden Hospital. He had multiple purpuric spots and hepatosplenomegaly. The Hb was 100%, the P.C.V. 58%, W.B.C. 12,000 per c.mm., and platelets 1,670,000 per c.mm. The serum-iron level was 84 μg. per 100 ml. Platelet survival studies with $DF^{32}P$ showed 12 days. The thromboplastic activity of the platelets was within normal limits (delayed formation of thromboplastin, but the final amount was at the lower limits of normal, especially when using high concentration). There was abnormal morphology of the platelets (10%), impaired clot retraction, and a slightly prolonged prothrombin-time. The bleeding-time was $6^1/_2$ minutes (Ivy), and the clotting-time 11 minutes.

The patient was treated with ^{32}P 5 mC intravenously. During the next 5 months he was well but the platelet-count was still high (765,000). The Hb was 108%, and the P.C.V. 61%.

He was given further treatment with ^{32}P 4 mC intravenously, and a good response was obtained: the Hb was 105%, P.C.V. 56%, W.B.C. 3700, and platelets 200,000.

Seven months later, when he presented with a large bruise following a slight knock, the hæmoglobin and hæmatocrit levels were higher than ever before: Hb 124%, R.B.C. 7,780,000, P.C.V. 60%, W.B.C. 5900, and platelets 257,000.

He was given a further 4 mC of ^{32}P intravenously, and when last seen, 18 months after the first treatment, the blood-count was normal.

Results

The platelet-survival times of the 17 patients investigated are shown in the table, together with the relevant data on sex, age, body-weight, and hepatic or splenic enlargement (if any).

PLATELET SURVIVAL IN HÆMATOLOGICAL AND OTHER CONDITIONS

Case no.	Diagnosis	Sex	Age (yr.)	Weight (kg.)	Clinical examination (enlargement in cm.)		Hb (%)	Hæmatocrit (%)	Blood-count (per c.mm.)			Platelet lifespan (days)
					Liver	Spleen			R.B.C. (million)	W.B.C. (thousand)	Platelets (thousand)	
6	Hodgkin's disease	M	48	64	0	0	97	..	..	15·5	323	8·0
7	Lymphosarcoma	M	45	65	0	0	77	..	..	2·5	145	6·0
1	Rodent ulcer	M	53	56	0	0	81	42	..	7·5	245	7·0
14	Fibrosarcoma	F	57	..	0	0	93	41	..	7·2	341	7·0
2	Polycythæmia vera	F	74	54	7	14	120	61	6·3	7·5	160	5·7
3	" "	M	58	53	4	7	157	86	8·6	14·0	177	5·2
9	" "	M	33	76	3	3·6	156	77	6·8	7·5	118	6·5
11	Polycythæmia vera (+ chronic myeloid leukæmia)	F	63	49	11	24	97	49	5·4	18·9	120	5·7
4	Polycythæmia vera	F	56	51	5	5	116	64	6·5	14·9	815	12·0
13	" "	F	72	50	0	14	100	54	6·6	36·5	559	10·5
15	" "	M	61	64	0	0	145	70	8·4	13·5	462	14·0
19	" "	F	65	56	6	10	108	52	5·4	8·4	552	11·7
10	Stress polycythæmia	M	39	76	0	0	112	49	5·7	5·6	218	10·2
16	Polycythæmia hypertonica	M	57	83	0	0	117	52	6·2	5·8	231	10·5
5	Thrombocythæmia	M	52	..	3·5	Splenectomised	95	46	4·9	9·4	1030	16·5
8	"	M	61	64	0	5	91	56	5·9	27·0	854	13·5
12	"	M	64	63	7	16	104	58	6·3	13·0	1134	12+

A patient with Hodgkin's disease, with a normal platelet-count (case 6) had a platelet lifespan of 8 days. In case 7, with lymphosarcoma and a persistently low platelet-count, the lifespan was 6 days. 2 patients (cases 1 and 14), with localised malignant growths and normal platelet-counts, had lifespans of 7·2 and 7 days respectively.

4 patients with polycythæmia vera (cases 2, 3, 9, and 11), who had low platelet-counts, had platelet lifespans of 5·7, 5·2, 6·5, and 5·7 days. 4 (cases 4, 13, 15, and 19) with high platelet-counts had platelet lifespans of 12, 10·5, 14, and 11·7 days respectively. Case 10 with stress polycythæmia, and case 16 with polycythæmia hypertonica, both had normal platelet-counts, and had platelet lifespans of 10·2 and 10·5 days.

3 patients with thrombocythæmia (cases 5, 8, and 12) and platelet-counts of 854,000–1,134,000 per c.mm. had platelet lifespans ranging from 12 to 16·5 days.

Discussion

The Normal Range

None of our subjects can be regarded as normal, and we have consequently accepted the normal lifespan of platelets as 8–10 days (Leeksma and Cohen 1956). We used $DF^{32}P$ obtained from the same source as these workers and we calculated the results, as they did, in terms of $DF^{32}P$ per 5×10^{12} platelets. When they calculated their results in terms of μg. of di-isopropyl-fluorophosphonate per g. of platelet nitrogen, they obtained normal values of 9–11 days, which agrees with the results reported by Pollycove et al. (1957) using the same method, and by Aas and Gardner (1958) with the radiochromium-labelling method for normal subjects.

Reticuloses

This group comprised a case of Hodgkin's disease (case 6) and one of lymphosarcoma of lymphoblastic cell type (case 7). In case 6 the peripheral-blood picture and red-cell survival were normal, and the platelet lifespan was also normal (8 days). In case 7 the bone-marrow showed lymphoid infiltration with reduced numbers of megakaryocytes. The peripheral-blood count was within the lower limits of the normal range, and the lifespan was reduced. This condition resembles that found in patients with polycythæmia vera and low platelet-counts (see below), where marrow infiltration is thought to give rise to disturbed megakaryocyte maturation and platelets of low vitality.

Localised Malignant Tumours

This group comprised 2 cases of primary malignant disease (case 1, rodent ulcer; case 14, fibrosarcoma of thigh). Both had normal peripheral platelet-counts and they were originally regarded as normal control subjects, but somewhat shortened survivals were in fact found, suggesting that malignant disease itself may be associated with an increased rate of platelet destruction. Malignant disease may affect the functions of proliferating tissues in general, so that platelets are produced with weakened vitality; or possibly, as suggested by Stefanini (1955), antibodies capable of cross-reacting to some extent with platelets are produced against malignant tissue.

Polycythæmia

The shortened lifespan found in 4 cases of polycythæmia vera with low platelet-counts (cases 2, 3, 9, and 11) could be due either to a defect in the mechanism of platelet production—resulting in platelets of low intrinsic vitality—or to over-activity of the spleen.

In case 9 there was evidence of diminution in the number of megakaryocytes in the bone-marrow, possibly as a result of crowding by the hyperplastic erythropoietic elements. Treatment with ^{32}P resulted in transient increases in peripheral platelet-counts. These observations support disordered megakaryocyte function as the explanation.

Case 11, in which polycythæmia vera led to chronic myeloid leukæmia, showed reduced platelet survival (5·7 days). 3 years previously this patient had had a reduced red-cell survival which was strongly suggestive of a hypersplenic state. This was supported by the bone-marrow picture of increased megakaryocytes and erythroid and myeloid elements.

The 4 cases with a raised platelet-count had either increased (cases 4, 15, and 19) or normal (case 13) platelet survival. The former in some respects resemble the thrombocythæmias, and are probably associated with a slow removal of platelets from the circulation.

The normal platelet lifespan in the patients with relative polycythæmia corresponds well with the normal platelet-count in the peripheral blood, the normal bone-marrow picture, and the absence of hepatosplenomegaly.

Thrombocythæmia

Many reports published recently have attempted to divide thrombocythæmia on an ætiological basis into "idiopathic or essential" and secondary. The first group includes those cases without apparent underlying disease, while the second group includes those associated with other myeloproliferative disorders (such as polycythæmia vera and myeloid leukæmia), myelosclerosis after splenectomy, and with splenic atrophy.

The two commonest manifestations of thrombocythæmia are a thrombotic and a hæmorrhagic tendency.

Hardisty and Wolff (1955) attempted to differentiate between hæmorrhagic and non-hæmorrhagic forms, defining the hæmorrhagic form as a condition in which the platelet-count remains above the upper limit of normal for months or years, in association with repeated episodes of spontaneous or excessive hæmorrhage. They reported 18 cases from the literature with such a condition, and added 5 more (one was our case 5). They tried to shed some light on the mechanism of the bleeding tendency by showing that qualitative defect of the platelets could be demonstrated by the thromboplastin-generation test which, they concluded, gives abnormal results only when thrombocythæmia is associated with abnormal bleeding.

Recently Shaw and Oliver (1958) reported 3 cases of primary thrombocythæmia associated with a hæmorrhagic tendency in which a similar abnormality was found in the platelets; but in another 3 cases of thrombocythæmia posthæmorrhagica no such abnormality was detected. Despite this Fountain (1958) detected no deficiency of platelet factor by the thromboplastin-generation test in 1 case of primary thrombocythæmia and 1 secondary to splenectomy.

In our series case 5 was associated with splenic atrophy, and cases 8 and 12 with polycythæmia vera. All showed bleeding and a thrombotic tendency. In case 5, a thromboplastin-generation test before gastrectomy showed significantly less thromboplastin formation than in the controls. On reinvestigation after gastrectomy (when the patient was free from bleeding symptoms and with a platelet-count still over a million) the result was normal.

Case 8 had a normal thromboplastin-generation test when free from bleeding symptoms. Only deficient clot retraction and a slightly prolonged prothrombin-time were observed. After a bleeding episode, the thromboplastic activity of the platelets was within normal limits, although formation of thromboplastin was delayed.

Morphological abnormality of the platelets was observed often (notably cases 5 and 12), though it was inconstant

and varied in degree. The abnormal appearance of the platelets could be related to their unusual production as demonstrated by hyperplasia of the megakaryocytes in the bone-marrow, which is the basis of Dameshek's (1951) concept of thrombocythæmia as one of the myeloproliferative syndromes in which excessive platelet production predominates. The good clinical and hæmatological response shown by these patients to ^{32}P therapy intended to reduce the megakaryocytic proliferation (Fountain 1958, Stefanini and Dameshek 1955, Friedman et al. 1956, Tubiana and Boiron 1957, Levin et al. 1957) supports this view and also adds to the general opinion that platelets are concerned intimately with the bleeding tendency.

Because many cases of thrombocythæmia arise after splenectomy and others are associated with splenic atrophy, attention has turned to the role of the spleen in such conditions. Hardisty and Wolff (1955) suggested that " the lack of a normal splenic function " in hæmorrhagic thrombocythæmia might partly explain the difference between this condition and other myeloproliferative disorders in which the platelets are relatively unaffected. This function, they suggested, might be concerned either with the inhibition of platelet production, or, more likely, with the removal of formed platelets from the circulation. Our studies, which suggested that thrombocythæmia is associated with a slow removal of platelets from the circulation, may throw some light on this problem.

Conclusions

These studies suggest that a reduced platelet lifespan may result from one of at least three causes—namely, (*a*) reduced vitality because of interference with megakaryocytic maturation; (*b*) increased function of the spleen, and conversely hypofunction causing prolonged survival (thrombocythæmia); or (*c*) the presence of autoantibodies. Possibly (*b*) and (*c*) are in effect manifestations of the same condition, since we do not know whether the action of the spleen in removing platelets from the circulation is " phagocytic ", or due to the elaboration of anti-platelet autoantibodies, or a combination of both.

Summary

Life-span determinations by the DF^{32}P method have been made on platelets in a variety of neoplastic and hæmatological diseases.

17 cases were investigated; these comprised 2 cases of reticulosis, 2 of localised malignant tumours, 10 of polycythæmia vera, and 3 of thrombocythæmia.

In polycythæmia, platelet life-span was reduced when the peripheral-platelet count was low and increased when the count was high.

In thrombocythæmia the lengthened life-span of the platelets suggests some impairment in the mechanism of removing platelets. The improvement in the clotting defect and the reduction of the platelet count following ^{32}P therapy confirms the intimate connection of the platelets with the bleeding tendency.

In the remaining neoplastic conditions survival-times were normal or slightly reduced.

Shortened platelet survival may be attributed to one of three causes—low platelet vitality, splenic hyperfunction, or the presence of autoantibodies.

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POSTOPERATIVE DIARRHŒA

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TRANSIENT diarrhœa after partial gastrectomy has been recognised clinically for many years (Howie et al. 1953, Bruce 1955). Characteristically the onset, during the early postoperative period, is sudden, all forms of treatment are unsuccessful, and spontaneous remission follows after a few days; culture of the stools fails to reveal any commonly recognised specific intestinal pathogenic organisms.

Similar diarrhœa may follow other gastric operations, especially vagotomy (Bruce 1955), and such procedures as colectomy and the relief of intestinal obstruction. The clinical aspects have been studied little, and, despite several bacteriological investigations (Howie et al. 1953, Duncan et al. 1954), the ætiology is unknown.

The Study

The kind of diarrhœa with which I am here concerned was diagnosed if a patient passed frequent watery stools for more than twenty-four hours during the first two weeks after operation, and bacteriological examination of the fæces revealed no specific intestinal pathogens. Patients who had had aperients were excluded, unless the interval before the onset of diarrhœa was such that the aperient could not have been responsible. All patients (393) under my observation who had abdominal operations during a three-year period (December, 1954, to November, 1957) at the Victoria Infirmary, Glasgow, ranked for inclusion in this study; of these, 51 had postoperative diarrhœa.

The clinical state before operation and the postoperative progress of the patients were recorded carefully. In 40 of the 308 gastric cases the electrolyte levels were estimated before operation and on the second and fifth postoperative days. In 100 gastric cases samples of gastric juice, aspirated on the first, the second, and sometimes the fifth postoperative days, were submitted to the Bacteriology Department of Glasgow University for examination. The intragastric tubes were boiled in water for ten minutes immediately before being passed, and during aspiration sterilised liquids only were given to the patient. Specimens were collected with sterile 20 ml. syringes (autoclaved for twenty minutes at 15 lb. per sq. in. pressure).

TABLE I—INCIDENCE OF POSTOPERATIVE DIARRHŒA

Operation	No. of patients	No. in whom diarrhœa developed
Relief of intestinal obstruction ..	27	16 (59%)
Colectomy	58	13 (23%)
Gastrectomy	163	12 (7%)
Gastroenterostomy and vagotomy ..	88	9 (10%)
Gastroenterostomy	57	1 (2%)
Total	393	51 (13%)

Bacteriological Examination

Each specimen was plated directly on to two blood-agar plates and on to MacConkey's medium, and a tube of Robertson's cooked-meat medium was also inoculated. One blood-agar plate was incubated anaerobically; all other media were incubated aerobically. After twenty-four hours' incubation the anaerobic blood-agar plates were examined for hæmolytic and non-hæmolytic colonies of *Clostridium welchii*. Further strains were isolated by plating the Robertson's cooked-meat medium on to blood-agar plates and incubating these anaerobically. The identity of all cultures of *Cl. welchii* was confirmed by showing that they produced α-toxin (lecithinase), and that this was neutralised specifically by *Cl. welchii* α-antitoxin. The MacConkey's medium was examined for specific intestinal pathogens, and the aerobically incubated blood-agar plate was examined for colonies of *Staphylococcus aureus*.

Clinical Features

Incidence.—Postoperative diarrhœa of unknown ætiology occurred in 51 (13%) of the 393 patients. The incidence depended greatly on the type of operation performed, as

TABLE II—INCIDENCE OF DIARRHŒA AFTER COLECTOMY AND RELIEF OF INTESTINAL OBSTRUCTION

Type of case	No. of patients	No. in whom diarrhœa developed
Colectomy:		
Preoperative succinyl sulphathiazole ..	41	7 (17%)
No preoperative preparation	17	2 (3·5%)
Relief of small-intestinal obstruction:		
Proximal jejunum	3	0 ..
Lower jejunum and upper ileum ..	3	1 (33%)
Lower ileum	8	6 (66%)
Relief of colonic obstruction by colostomy:		
Ileocæcal valve competent	4	0 ..
Ileocæcal valve incompetent	9	9 (100%)
Controls:		
Colostomy for non-obstructive lesions	21	1 (5%)

table I shows. Diarrhœa did not follow any other abdominal operation, unless there was paralytic ileus.

Onset.—This was usually abrupt and usually on the fourth to seventh postoperative day. 2 patients were affected severely as early as the second day; 1 of these died within twenty-four hours of the onset of diarrhœa, and necropsy revealed the typical features of necrotising enteritis. But usually the diarrhœa was mild, not causing undue anxiety.

Duration.—The duration was from two to ten days (mean 4·2±1·8 days). Recurrent attacks were observed in 2 cases only.

Seasonal prevalence.—The cases were scattered almost uniformly throughout the year. 27 arose during the summer months (April–September) compared with 24 during the winter.

Possible Ætiological Factors

Antibiotics.—These were given, either before operation or early in the postoperative period, to 25 (49%) of the 51 patients in whom diarrhœa developed, compared with 174 (51%) of the 342 patients without this complication. Thus antibiotics did not influence diarrhœa in this series. But succinyl sulphathiazole seemed to reduce the incidence in patients who underwent colectomy (table II).

General nutrition and electrolyte balance.—In the most severe cases of electrolyte imbalance (i.e., those with pyloric stenosis), gastroenterostomy was nearly always performed. As table I shows, diarrhœa arose after this operation much less often than in the series as a whole. This suggests that neither malnutrition nor electrolyte imbalance were, by themselves, important in causing postoperative diarrhœa. Routine electrolyte estimations, therefore, were discontinued.

Operative or postoperative hypotension.—23 patients had definite hypotension (below 90 mm. Hg systolic) during or after operation. Diarrhœa developed in 3 (13%) of these, but they had intestinal stasis also. There was no evidence, therefore, that hypotension per se was an ætiological factor.

Intestinal stasis.—323 patients were placed in three groups according to the degree of stasis detected clinically

TABLE III—RELATION OF POSTOPERATIVE DIARRHŒA TO INTESTINAL STASIS

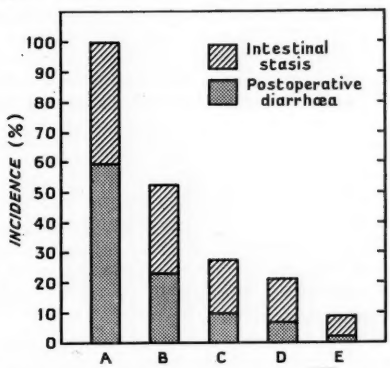
Clinical type	Total no. of patients	No. in whom diarrhœa developed	No. without diarrhœa
No stasis	216	11 (5%)	205 (95%)
Slight stasis ..	66	11 (17%)	55 (83%)
Severe stasis* ..	41	21 (51%)	20 (49%)
All types ..	323	43 (13%)	280 (87%)

* Includes all cases (27) of intestinal obstruction.

(table III). 70 were excluded because of insufficient data. All those with acute intestinal obstruction were placed in the third group. The incidence of postoperative diarrhœa was related closely to the degree of intestinal stasis, and this relation was statistically highly significant. Diarrhœa invariably followed recovery from complete intestinal stasis (paralytic ileus); and after an abdominal operation diarrhœa and intestinal stasis were directly proportional (see figure).

Level of obstruction.—Further analysis of the cases of intestinal obstruction (table II) showed that diarrhœa after relief of small-intestinal obstruction was related to the level of obstruction; the lower the obstruction, the greater the incidence of diarrhœa. In patients with large-bowel obstruction relieved by colostomy, diarrhœa developed only when the ileocæcal valve had been found incompetent at operation.

Bacteriology of stomach contents.—Table IV shows the results of bacteriological examination of the gastric juice of 100 patients after gastric operations. *Cl. welchii* was isolated from 16 patients, in 14 of whom intestinal stasis developed. *Escherichia coli* was isolated from 23 of the



Relation of postoperative diarrhœa to intestinal stasis.

Column A = cases of intestinal obstruction
„ B = „ „ colectomy
„ C = „ „ vagotomy
„ D = „ „ gastrectomy
„ E = „ „ gastroenterostomy

TABLE IV—BACTERIOLOGY OF GASTRIC ASPIRATE IN 100 PATIENTS AFTER GASTRIC SURGERY

Clinical type	Organisms cultured from gastric contents						No. of patients
	Esch. coli	*Cl. welchii*	*Staph. aureus*	*Str. β-hæm.*	Others*	Nil	
Intestinal stasis	23	14	3	3	9	3	27
Gastric retention	2	0	0	0	0	3	5
Uneventful	20	2	5	6	24	39	68
Total ..	45	16	8	9	33	45	100

* Includes anthracoids, streptococci, proteus, and yeasts.

27 patients with clinical evidence of stasis, and also from 20 patients without such evidence. Other organisms appeared only sporadically, and none was associated particularly with intestinal stasis. Of the 100 patients diarrhœa developed in 6, and in each *Cl. welchii* and *Esch. coli* were cultured from the stomach remnant after operation.

Discussion

In reviewing the records of 1700 patients after partial gastrectomy, Dawson-Edwards and Morrissey (1955) found that 35 (2%) had postoperative diarrhœa (excluding cases incompletely documented). They found no evidence of hypotension before the onset of symptoms. The factors common to all cases were a major surgical procedure, with consequent restriction of food and fluids, and a variable period of intestinal stasis.

Shipman (1959) suggested that diarrhœa in subacute intestinal obstruction was due to " intestinal hurry " as a result of increased peristalsis, leading to failure of the colon to reabsorb water. But it is difficult to see how an obstructive lesion could cause intestinal hurry, especially as dilated loops of bowel were seen radiologically and at operation in all patients—which is surely good evidence of intestinal stasis.

Several investigators have shown that the jejunum and upper ileum contain very few bacteria compared with the lower ileum and colon (Kendall et al. 1927, Cregan and Hayward 1953, Duncan et al. 1954). Experimental evidence (Bullen et al. 1953) suggests that the main factors in maintaining the relative sterility of the upper intestine are the low pH of the stomach and the rapid passage of intestinal contents through the small bowel. The low pH sterilises the alimentary contents before they enter the jejunum, and the rapid emptying prevents any surviving organisms from colonising the jejunum. Normal intestinal peristalsis also prevents colonic organisms from invading the upper intestine; within a few hours of death these organisms rapidly colonise the upper jejunum (Blacklock et al. 1937), presumably because peristaltic movements have ceased. Any intestinal stasis or bowel obstruction must weaken this mechanical barrier, which in paralytic ileus or complete intestinal occlusion will be completely neutralised.

In this series, postoperative diarrhœa was closely related to (1) intestinal stasis after abdominal operations, (2) relief of low small-intestinal obstruction, and (3) relief of colonic obstruction when the ileocæcal valve was incompetent. These conditions all favour the upward migration of lower-intestinal organisms, and this suggests strongly that transient colonisation by colonic organisms of the normally almost sterile jejunum is the most important factor leading to postoperative diarrhœa.

This view is supported by the familiar observation that patients with gastrocolic fistulæ often have intractable diarrhœa, due to constant contamination of the jejunum by colonic contents (Pfeiffer and Kent 1939), and relieved by a proximal defunctioning colostomy. It explains why patients with high intestinal obstruction are not so prone to postoperative diarrhœa as those with low intestinal obstruction, and why patients with colonic obstruction have postoperative diarrhœa only if the ileocæcal valve is incompetent.

Coagulase-positive staphylococci have been incriminated in several recent small epidemics of diarrhœa after abdominal operations (Dearing and Heilman 1953, Cook et al. 1957, Webster 1958). All the cases described by these workers had had antibiotics prophylactically, and the diarrhœa was nearly always severe, with a high mortality-rate. These cases were most unlikely to be related ætiologically to the present series, in which the cases of diarrhœa were sporadic and mild. Coagulase-positive staphylococci were not isolated from the stools of the cases in my series, though no special enrichment technique was used. But the isolation of a few coagulase-positive staphylococci from the stools has little significance, because many normal patients excrete them from time to time, especially in hospitals (Brodie et al. 1956). In all the cases of staphylococcal diarrhœa reported by Webster (1958), enormous numbers of organisms and pus-cells were found in the stools.

Howie et al. (1953) investigated the stomach aspirates of postgastrectomy patients soon after operation and isolated *Cl. welchii* from 12 of 15 patients. The presence of *Cl. welchii* in the stomach clearly did not correlate with postoperative diarrhœa. In the present series *Cl. welchii* was isolated from only 14 of 100 patients; 12 of the 14 showed signs of intestinal stasis, and diarrhœa developed in 6. *Esch. coli* was associated more commonly with intestinal stasis, but it was cultured also from many patients without clinical evidence of stasis. *Esch. coli* may possibly spread up the alimentary canal during minor episodes of stasis which are not always detectable clinically, whereas *Cl. welchii* spreads only when the stasis is more complete.

But it is far from certain that *Cl. welchii* should be accepted as the causal organism in postoperative diarrhœa. Many different organisms, or a combination of organisms, if introduced into the jejunum under appropriate conditions, may be capable of producing a reaction resulting in diarrhœa.

The possible role of viruses remains to be investigated. An important point is that disorders of intestinal motility influence the intestinal bacterial flora, both in numbers and species. Thus the relation is complex, with many possible interactions.

Summary

Postoperative diarrhœa developed in 51 of 393 patients who had abdominal operations over a three-year period.

The incidence was greatest after relief of intestinal obstruction; less high after colectomy, gastrectomy, and vagotomy; and low after gastroenterostomy.

Nearly all cases in which diarrhœa developed showed clinical evidence of intestinal stasis. No other common factor was found.

The gastric aspirate was studied bacteriologically in 100 cases after gastric operations. The only organisms associated with intestinal stasis were *Escherichia coli* and *Clostridium welchii*.

Proliferation of *Cl. welchii* might be responsible in some way for the diarrhœa.

I am greatly indebted to Prof. J. W. Howie and Mr. Robert Mailer for their helpful interest and criticism, and to Dr. Sheila McDonald and Mr. D. B. Colquhoun for the bacteriological investigations. The patients were under the care of Mr. Ian Macpherson, Mr. Robert Mailer, and Mr. Hinton Robertson.

References at foot of next column

HYPOTHERMIA AND HYPOTENSION DURING CRANIOTOMY IN A PREGNANT WOMAN

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DURING the past 5 years, hypothermia has been induced in 306 patients admitted to the Regional Neurosurgical Centre at Walton Hospital, Liverpool. Despite this experience in patients of each sex, ranging from infants to old people, it was only in December, 1958, that we were confronted with the problem in advanced pregnancy. This woman had had a spontaneous intracranial hæmorrhage from a congenital "berry" aneurysm, and urgent operation was considered necessary.

We know of only 1 other pregnant patient (Rowbotham et al. 1957) treated by hypothermia following an intracranial lesion. After a severe head injury she was cooled for 7 days, the rectal temperature being kept at 30–34°C. At the time of injury she was 8 weeks pregnant, and 28 weeks later she was delivered normally of a healthy infant.

Our patient went into labour 29 hours after craniotomy had been performed under hypothermia and hypotension. 2 hours later she gave birth to a normal female infant weighing 4 lb. 8 oz.

Case-report

A woman, aged 31, had six living children. She was admitted to a psychiatric unit in December, 1958, when she was 32 weeks pregnant. She had had frequent headaches for 6 months. There was no evidence of toxæmia of pregnancy; the blood-pressure was 170/75 mm. Hg and it later fell to 110/60 as her symptoms subsided.

Several hours before admission to hospital sudden severe generalised headache and pain in the neck had developed. Later she became restless and slightly confused, shouting "Am I going mental? Have I got a cerebral hæmorrhage?" Her mother had died from a "cerebral catastrophe". The patient was thought to have an anxiety neurosis, but a physician, called in consultation, discovered neck rigidity and positive Kernig's signs. One of us (C. B. S.) was asked to see her, and she was transferred to the neurosurgical unit. Lumbar puncture revealed a heavily bloodstained cerebrospinal fluid. She was slightly dysphasic, and, as she was right-handed, a spontaneous intracranial hæmorrhage on the left was diagnosed.

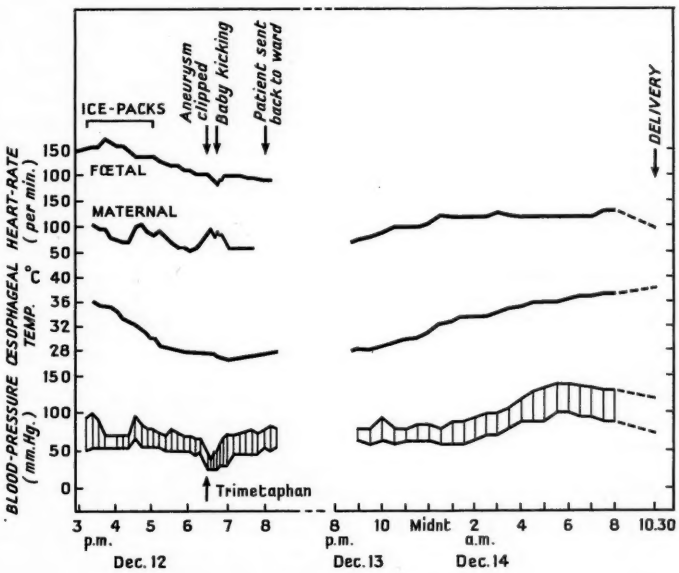
Angiography

Bilateral carotid angiography, with the routine angiographic estimation of the collateral circulation through the anterior segment of the circle of Willis, was performed under general anæsthesia (Sedzimir 1959). The angiograms confirmed the presence of an aneurysm situated on the bifurcation of the left internal carotid artery. Surprisingly, there was no spasm of the cerebral arteries nor any evidence of an intracranial hæmatoma. The collateral circulation was excellent. In view of these findings an urgent craniotomy was considered essential.

Operation (Dec. 12)

The technique employed in anæsthetising the patient closely resembled that advocated by McBurrows et al. (1956).

3.0 p.m.—Anæsthesia was induced by sodium thiopentone, followed by suxamethonium chloride for relaxation, and maintained with nitrous oxide, oxygen, and ether. Cooling was started by laying the patient on a large polyethylene bag containing ice, after which 12–20 ice-bags were placed over the anterior surface of the body. The temperature was taken via œsophageal and rectal leads with an electric thermometer (spot-galvanometer thermocouple). The pulse, temperature, blood-pressure, and fœtal heart-rate were recorded every 10 minutes (see figure).



Recordings made during and after craniotomy.

During the cooling process the fœtal heart-rate dropped constantly with the maternal temperature. This was in accordance with the findings of Smyth and Farrow (1958) that cooling slowed the heart-rate of a fœtus removed by hysterotomy.

5.5 p.m.—When the temperature had fallen to 30°C the ice-packs were removed and the patient was transferred to the theatre. The maternal pulse-rate was then 85 per minute and the blood-pressure 80/55. The fœtal heart-rate was 130 per minute. Because of the need for diathermy the ether was discontinued and trichloroethylene was introduced into the circuit. The internal carotid artery was exposed in the neck and a rubber catheter was placed around it to assist in controlling hæmorrhage if it occurred.

5.45 p.m.—The pulse-rate was 56 per minute, blood-pressure 70/50, fœtal heart-rate 112 per minute. The uterus appeared fairly flaccid in that the fœtal parts could readily be distinguished. A left frontotemporal craniotomy was performed, the ventricle was tapped, and about 50 ml. of fluid was withdrawn. The frontal lobe was easily retracted exposing the optic nerve

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and internal carotid artery. As soon as the level of the carotid bifurcation was reached, brisk hæmorrhage issued from the aneurysm, which was still invisible. The catheter was tightened to occlude the artery, but the intensity of the hæmorrhage was unaffected. A temporary clip was then applied over the internal carotid artery just below the bifurcation, and the hæmorrhage practically ceased. The aneurysm was exposed quite easily and a large tantalum clip was placed across it, close to its neck, but not involving the origin of the middle cerebral artery. When the temporary clip on the internal carotid artery was removed the middle cerebral artery was seen to be pulsating normally.

At the time of the brisk hæmorrhage from the aneurysm, the blood-pressure recorded by the oscillometer was 65/50. An 0·2% solution of trimetaphan was transfused immediately into the patient's arm via a three-way tap, already connected to an intravenous drip, and the blood-pressure was reduced to 40/25. This concentration of trimetaphan was higher than is normally used because of the occasional difficulty in lowering the blood-pressure of young patients. Within 5 minutes of hypotension being established the maternal pulse-rate had risen to 95 per minute, and the fœtal heart-rate had fallen to 85 per minute, the sounds becoming more distant to auscultation. The trichloroethylene was turned off, and the uterus was found to be stony hard making it difficult to palpate the fœtal parts. Once the aneurysm had been clipped the systolic pressure remained at 40 mm. Hg for 8–10 minutes, and then it rose to 60 mm. Hg after the rapid transfusion of a pint of blood. With the rise in blood-pressure the fœtal heart-rate increased to 100 per minute, but the heart-sounds were still less distinct than previously, and the fœtus was extremely active in its movements.

Closure of the skull was uneventful; $^3/_4$ of an hour before the end of the operation the nitrous oxide was turned off and the flow of oxygen was increased. On completion of the operation, the uterus remained hypertonic but the fœtal heart-sounds were a little more distinct. The mother's blood-pressure was 80/50, and after removal of the endotracheal tube she moved her legs and groaned. Vaginal examination showed the cervix to be patulous. She was sent back to the ward at 8 P.M.

Progress

Next morning the fœtal heart was easily audible, and at 6.30 P.M. the patient was having definite uterine contractions associated with slowing of the fœtal heart-rate from 160 to 126 per minute.

8.30 p.m.—Vaginal examination showed the cervix to be 2-fingers dilated.

9.30 p.m.—The cervix was 3-fingers dilated, with the fore-waters bulging through the cervical os.

10.15 p.m.—The membranes were ruptured artificially; the liquor was clear with no meconium staining.

10.30 p.m.—A living child, who cried well, was delivered normally.

10.40 p.m.—The third stage of labour was complete, with normal blood-loss. (This suggests that the hypothermia had not interfered to any great extent with the clotting mechanism at the time of delivery.)

The patient's postoperative and postpartum progress was entirely uneventful. Her dysphasia, which was slight before operation, became more severe but she could express herself by short sentences. Speech comprehension was normal. There was no paralysis of the limbs. She was discharged home fully ambulant 38 days after operation. She is having speech therapy at the Royal Southern Hospital, Liverpool. To date the baby thrives, and shows no abnormality.

Discussion

The uterine hypertonicity and the excessive fœtal movements are difficult to explain.

Hypertonicity of the Uterus

In estimating uterine tone, measurement of the intra-amniotic pressure is desirable but in this case the hypertonicity was a clinical observation, assessed by palpation. Palpation through the abdominal wall may be misleading because of resistance by the abdominal muscles. In this patient, however, the voluntary muscles, including those of the abdominal wall, seemed to be flaccid (which is to be expected under such anæsthesia). We think, therefore, that our assessment of the state of the uterus was reasonably accurate. We do not know exactly when the uterus became hypertonic; until the incision was made (when the maternal temperature was 28·8°C) the fœtal parts could be felt easily and the uterus was flaccid. It was not palpated again until the temperature was 27·9°C (5 minutes after starting the infusion of trimetaphan), when it felt solid, and the fœtal parts could no longer be distinguished.

Pronounced hypertonicity may have arisen because the uterus contracted in direct response to the action of cold between temperatures of 28·8°C and 27°C; but this seems unlikely with such a slight fall in maternal temperature. Alternatively the uterus may have contracted and then remained hypertonic in response to the hypotension produced by the trimetaphan.

Although Hendricks (1958) showed that estimations of volume redistributions were equivocal during the infusion of oxytocin, initial uterine contraction in our case may have been a response to the maternal hypotension, which would increase the venous return. The extra 300 ml. of blood ejected into the general circulation would tend to restore the blood-pressure to a more satisfactory level.

The volume of blood contained in the uterus at term has never been determined accurately, though Barcroft and Rothschild (1932) believed it may be 500–600 ml. But other workers—e.g., Woodbury et al. (1944)—think it may be as much as 1 litre. Assali et al. (1953) catheterised the uterine vein in a normal subject at term, and estimated the uterine blood-flow at around 750 ml. per minute. Browne (1954), by radioactive-clearance methods, obtained the relatively low figure of 600 ml. per minute.

It seems that the uterus and placenta contain a vast quantity of blood, and if pooling occurred (as it tends to do in the maternal circulation after trimetaphan) these structures may well act as a huge reservoir literally draining the maternal circulation and causing profound circulatory collapse. The uterine hypertonicity therefore may have been a response to the maternal hypotension, consequently preventing the pooling of blood.

Excessive Fœtal Movements

Within 5 minutes of giving trimetaphan the fœtus was kicking violently. These excessive movements may have been due to fœtal hypoxia.

The pressure in the intervillous spaces is thought to vary between 10 and 40 mm. Hg according to the degree of uterine tone. In our patient the systolic pressure was 60–65 mm. Hg before trimetaphan was given. This difference in pressure between the mother and fœtus would enable fresh blood to be supplied to the fœtal circulation. When trimetaphan was infused and the systolic pressure fell to 40 mm. Hg the pressure gradient may have been insufficient to supply oxygenated blood to the fœtus, especially if the uterine outflow was occluded. But when the maternal pressure rose to 65–70 mm. Hg after rapid transfusion and discontinuation of the trimetaphan drip, oxygenated blood may again have been able to reach the fœtus, thus restoring the fœtal heart-rate to its previous level.

If the movements were due to hypoxia, we have to explain how the fœtus survived under these conditions. Despite the uterus pumping 300 ml. of blood into the general circulation we think that the pressure on the

myometrial veins and placental sinuses would prevent the uterus and placental site from emptying completely. In fact a high proportion of the vascular contents must have been trapped. During the uterine hypertonus the fœtus, because of its low rate of metabolism, may, however, have survived on this trapped blood.

Fœtal Activity at Low Temperatures

France (1957) showed that newborn infants were active and able to cry at temperatures as low as 28·6°C. In this case, however, the infant should have been anæsthetised by the nitrous oxide and trichloroethylene, and we cannot explain why movements occurred under these conditions.

Effect of Hypothermia on Onset of Labour

Hypothermia may have caused the mother to go into premature labour. Perhaps venous stasis at the placental site resulted in thrombosis or infarction, so that there was placental insufficiency. It would have been interesting to have investigated placental function by measuring the urinary œstrogens before and after operation to determine whether there had been any interference with placental efficiency. On the other hand, the onset of labour may have been due to the operation itself. In our recent experience 2 women subjected to exploratory burr-holes went into labour on the night of operation. One was normothermic when operated on, and was found to have cortical thrombophlebitis; the other had a pyrexia of 102°C, and was later found to have tuberculous meningitis.

In the present case, as the patient did not go into labour until 29 hours after craniotomy—a much more severe operation—the hypothermia may have antagonised the tendency to abort immediately after surgical interference to the brain in late pregnancy.

Summary

A multiparous woman, when 32 weeks pregnant, had hæmorrhage from an intracranial aneurysm, which necessitated urgent craniotomy under hypothermia and hypotension. She went into labour 29 hours later, giving birth to a normal child, although there had been long-continued uterine hypertonicity and excessive fœtal movements towards the end of the operation.

We wish to thank Prof. T. Cecil Gray and Mr. H. H. Francis for their advice and helpful criticism, and Mrs. Ursula Todd and Mr. W. Lee for help with the figure.

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"... Almost all the children who are sent to approved schools have some degree of emotional disturbance; the degree of severe neurosis is very high. Over the last two years it has also been markedly increasing; no one is quite sure why. 'The degree of insecurity and emotional disturbance in our boys has become fantastic,' said one headmaster. Another said: 'A few years ago we were getting the real tough eggs. They were easy to handle because you could get a response out of them. Now they are all so apathetic, frustrated, closed in you simply cannot get any response at all.' "—ROY PERROTT, *The Guardian*, Nov. 16, 1959.

MANAGEMENT OF CHRONIC LUMBOSACRAL STRAIN

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IN a previous report (Bremner 1958) the place of manipulation under general anæsthesia as a first step in the management of patients with lumbosacral strain was discussed, and the short-term results of such treatment were reviewed. The term "lumbosacral strain" was defined, and the limited objectives of active hospital treatment were specified. The results were on the whole satisfactory, the manœuvre providing a reasonable method of treating such patients actively. But this has not been the universal treatment for such cases in the orthopædic department of the Middlesex Hospital; about half our patients have had physiotherapy without formal manipulation under anæsthesia. Using the subjective criteria previously adopted (Bremner 1958) we describe here the results in 150 consecutive patients treated primarily by this alternative technique, and compare these results with those obtained by manipulation under general anæsthesia.

Clinical Material

48 males (average age 40) and 102 females (average age 37) were studied. The sex-ratio, of about 2 females to 1 male, and the average ages correspond very closely to those of the previous group.

Management

Physiotherapy was given three times weekly in the form of deep massage to the lumbosacral region, localising any tender spots. If there was much spasm, short-wave diathermy was also applied. The spine was then manipulated in rotation, after the method suggested by Wiles (1956), and a scheme of exercises to mobilise the spine and to increase muscle power was instituted. The patient should keep up these exercises on his own indefinitely after completion of active treatment. Instruction given on management of the back in everyday life was regarded as most important.

Assessment of Results

The patients were reviewed after 4 weeks' treatment and subjectively classified as follows:

Group I, "*cured*": complete relief of all back symptoms.

Group II, "*improved*".

(1) Much improved, to a degree where the patient felt that no further active treatment was required, although some residual symptoms persisted.

(2) Some improvement, but symptoms which the patient considered significant were still present, progressing to group II (1) after further physiotherapy.

(3) As in group II (2) but adequate comfort attained only by wearing a lumbosacral corset.

Group III, "*no change*".

Group IV, "*worse*".

This is the classification used before except that the subclassification of groups III and IV, which had little value, has been omitted. The table shows the results in the present series compared with those of the previous series managed by manipulation under general anæsthesia.

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RESULTS OF TREATING CHRONIC LUMBOSACRAL STRAIN

Group	Present series (150 cases). Treated by physiotherapy		Previous series (250 cases). Manipulated under general anæsthesia	
I	12 (8%)	(54·7%)* (87·4%)†	25 (10%)	(64·4%)* (86·8%)†
II (1)	70 (46·7%)		136 (54·4%)	
(2)	34 (22·7%)		20 (8%)	
(3)	15 (10%)		36 (14·4%)	
III	7 (4·6%)	(12·6%)‡	24 (9·6%)	(13·2%)‡
IV	12 (8%)		9 (3·6%)	

* Discharged at the first post-treatment visit.
† Total gaining any benefit from treatment.
‡ Not improved or worse.

Discussion

The composition of these two series as regards sex-distribution and average age is very similar; this supports the idea of a specific condition called "lumbosacral strain" despite the vague diagnostic criteria.

The results of treatment by the two methods are remarkably similar, the only significant difference being in group II (2) (i.e., patients who had improved at the first review but who still had symptoms which settled after further treatment). This group was considerably larger in the present series, as might be expected. Many patients enjoy their physiotherapy, and when, at first review, they are still improving and ask to continue treatment, there is a natural tendency to agree, the course of treatment being less "definitive" than a single manipulation under general anæsthesia.

The similarity of these results may well raise doubts as to the specificity of either form of treatment. One might argue that we are assessing "applied psychotherapy" in different forms in a condition where the patient's outlook seems to influence the symptoms. A form of "control" treatment equally convincing to the patient but not involving physical attention to the back would be difficult to devise.

Treatment by physiotherapy is considerably more demanding on time, facilities, and personnel in the physiotherapy department than the alternative technique, and somewhat more demanding on clinic time in as much as 10% more patients had to be seen again after the first post-treatment visit. On the other hand, these patients were spared the slight risk and possible discomforts of a general anæsthetic.

It would be interesting to know whether the period of "cure" differs after the two methods, but the many variables made attempts at assessment too difficult. We believe that subsequent freedom from trouble depends much more on the patient's ability to "learn to live with his back" than on the treatment given. This point must be stressed repeatedly in dealing with these patients.

Some patients might do better with the one form of treatment and some with the other. These series were not selected with this point in mind, but because of the preference of the consultant surgeon concerned; they therefore represent a random selection for each form of management. No points have arisen to suggest that one method rather than the other is specifically indicated, or more likely to be effective, in any recognisable subgroup.

On its face value the evidence suggests that the alternatives are equally satisfactory in their immediate result. Which is chosen must depend considerably on the facilities of the department and in particular on the physiotherapeutic services available.

Summary

150 consecutive patients with chronic lumbosacral strain were treated by physiotherapy without formal manipulation under anæsthesia. After 4 weeks 55% were cured, 32% had improved, and 13% were unchanged or worse.

There was little difference between the results of this form of treatment and the results of management by manipulation under general anæsthesia in a previous comparable series. The patient's ability to "live with his back" seems to be more important than the form of treatment.

Our thanks are due to Mr. Philip Wiles and Mr. P. H. Newman, under whose care these patients were, for permission to publish this report.

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PULMONARY DECORTICATION

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ALTHOUGH Delorme described pulmonary decortication in 1896, it was not until the second world war that the need to expand the lung of patients with traumatic clotted hæmothorax provided a real stimulus (Lush et al. 1944, Nicholson 1946, Burford et al. 1945). In 1947 Gurd described 3 cases of tuberculous pleuritis treated by decortication; and, despite critical reception, more and more similar reports followed (Himmelstein et al. 1948, Lam 1948). By 1949 streptomycin cover was being used (Weinberg and Davis 1949); and since then decortication either by itself or combined with resection or thoracoplasty, has become accepted as a safe and effective treatment of the pleural complications of pulmonary tuberculosis. In a study of 43 cases Savage and Fleming (1955) demonstrated the effectiveness of the method and laid stress on the importance of early postoperative lung expansion.

This paper records the results of decortication in 27 patients (see table I). The operations were performed by one of us (J. D.) during the past four years.

Material

17 of the patients had pleural tuberculosis, with or without underlying parenchymal disease; and they had had various forms of antituberculous treatment, including chemotherapy, artificial pneumothorax, thoracoplasty, and pulmonary resection. Their ages ranged from 16 to 47. Cases 11 and 26 had a lobectomy at the time of the decortication. All patients had repeated aspirations of pleural fluid and some received intrapleural antibiotics. In 5 cases an effusion had been present for more than ten years.

The Operation

Blood was transfused in all cases to replace loss during and after operation. No attempt was made to stay outside the empyema cavity, but care was taken to remove all pieces of granulation tissue. In all patients the parietal and diaphragmatic peels were removed. The plane of cleavage on the surface of the lung was external to the visceral pleura. Ease of stripping bore no relation to the duration of the effusion: it was largely unpredictable. Sometimes it was necessary to leave postage-

stamp size of peels immediately overlying parenchymatous disease.

Routine use of a double-lumen Carlen's anæsthetic tube simplified the operation: it allowed the dissection to be carried out on either collapsed or expanded lung, as circumstances dictated. Postoperatively two tubes were left in the chest: they were connected to underwater-drain bottles to which continuous suction was applied and they continued to drain until all the air-leaks had sealed and the lung had expanded. This rarely took longer than four days. Hyperextension, as advocated by Savage and Fleming (1955), was not used.

Results

Clinical

Every surviving patient has been examined within the past three months. There were no operation deaths or complications; and only 1 man died later—three years after the operation, from an unknown cause.

Obliteration of the pleural space by expanded lung was achieved in every case, though radiologically there was slight residual pleural thickening in a few. All patients enjoyed better general health and a subjective increase in respiratory function.

Lung-function Studies

Ventilatory studies were carried out in 10 unselected patients before and after operation. All suffered from tuberculosis. With 1 exception the postoperative measurements were made after a three-month interval. Table II shows that ventilation was strikingly improved in every case except case 2. This patient had his postoperative tests within a month of operation. The actual volumes have approached those expected on the basis of height and weight (Dubos).

Discussion

The aim of the operation is to rid the patient either of a dangerous space or of a collection of infected material, and at the same time to improve lung function. These aims can be applied to a recent empyema or clotted hæmothorax, as well as to such longstanding conditions as an unobliterated pneumothorax or a chronic tuberculous empyema. Cases of primary tuberculous effusion without uncontrolled parenchymatous disease should also be submitted to this type of surgery if they do not respond to conservative treatment.

Whilst it is known that some patients with a residual effusion after artificial pneumothorax remain in good health for many years, their respiratory function is diminished, and not uncommonly serious or fatal complications ensue. A persistent collection of fluid in the chest spells constant insecurity. Such patients are likely to develop respiratory distress during episodes of respiratory

TABLE I—CONSECUTIVE CASES OF PULMONARY DECORTICATION

Case no.	Disease *	Duration (months)	Sputum	Nature of pleural fluid	Antibiotics †	Histology
1	Primary effusion	9	−ve	Serous	S. P. H.	..
2	Post-A.P. empyema	108	+ve	Pus	S. P. H.	Chronic inflammatory
3	Primary effusion	8	−ve	Serous	S. P. H.	Chronic inflammatory
4	Post-A.P. empyema	96	+ve	Pus	S. P. H.	Chronic inflammatory
5	Secondary empyema	8	−ve	Pus	S. P. H.	Chronic inflammatory
6	Primary effusion	192	−ve	Serous	S. P.	Tuberculous granulation
7	Primary effusion	5	−ve	Serous	S. P. H.	Tuberculous granulation
8	Post-A.P. empyema	40	+ve	Pus	S. P.	Tuberculous granulation
9	Secondary empyema	6	+ve	Pus	S. P. H.	..
10	Primary effusion	7	−ve	Pus	S. P. H.	Chronic inflammatory
11	Secondary empyema	16	+ve	Pus	S. H.	..
12	Post-A.P. empyema	31	+ve	Pus	S. P. H.	Chronic inflammatory
13	Secondary empyema	12	+ve	Pus	S. P. H.	..
14	Post-A.P. effusion	144	+ve	Serous	S. P. H.	Chronic inflammatory
15	Post-A.P. effusion	12	−ve	Serous	S.	..
16	A.P. cavity rupture	1	+ve	Pus	S. P.	Caseous
17	Post-pn. empyema	1	−ve	Pus; gram +ve cocci	Pen.	Chronic inflammatory
18	Post-pn. empyema	2	−ve	Pus; staphylococci	Pen.	Inflamed pleura
19	Hæmorrhagic basal effusion following trauma; fractured rib and sternum	2	−ve	Blood; no pus	Pen.	..
20	Empyema following effusion	3	−ve	Blood-stained pus; gram +ve and −ve cocci	Pen.	..
21	Post-pn. empyema	24 yr.	−ve	Pus	Pen.	Fibrous thickened pleura
22	Post-A.P. empyema	16 yr.	−ve	Pus	S.	Thick fibrous pleura
23	Post-traumatic hæmorrhagic effusion	3 weeks	−ve	Blood	Pen.	Fibrous pleura
24	Post-pn. effusion	4	−ve	Serous	Pen.	Thickened dense pleura
25	Post-pn. empyema	1½	−ve	Pus	S. Pen.	Thick inflammatory reaction with fibrosis
26	Post-A.P. empyema	6 yr.	−ve	Pus	S. Pen.	Thick inflammatory reaction with fibrosis
27	Post-A.P. empyema	10 yr.	+ve	Pus	S.	Thick inflammatory reaction: tuberculous caseation

* Post-A.P.: following artificial pneumothorax. Post-pn.: post-pneumonic. † S: streptomycin. P.: *p*. aminobenzoic acid. H.: isoniazid. Pen.: penicillin.

TABLE II—LUNG FUNCTION IN 10 PATIENTS BEFORE AND AFTER DECORTICATION

Case no.	Age (yr.)	Ventilatory capacity (litres)			Max. breathing capacity (litres)			Preop.	Postop.
		Predicted	Actual		Predicted	Actual			
			Pre-op.	Post-op.		Pre-op.	Post-op.		
1	23	3·4	2·5	3·1	90	78	86		
2	30	4·1	3·8	3·8	110	86	110		
3	46	4·8	3·0	4·1	140	80	134		
4	37	3·6	2·5	3·3	110	75	104		
5	48	3·0	2·2	2·5	92	68	80		
6	34	4·1	3·1	3·8	136	105	126		
7	37	3·6	2·3	2·8	96	30	80		
8	21	3·6	2·7	2·9	110	85	100		
9	16	3·7	3·0	3·6	128	104	126		
10	35	3·9	2·0	3·5	130	68	97		

infection; and secondary infection of the pleural fluid and the development of a bronchopleural fistula are additional hazards.

Gordon and Wells (1949) found no consistent improvement in lung function after decortication in tuberculous patients; but Patton et al. (1952) showed that, whereas immediately after operation there was little or no improvement, a follow-up showed substantial increase in ventilation.

Thomas and Jarvis (1956) emphasised the importance of removing the parietal and diaphragmatic pleura, and they showed that results are best in patients whose lungs are least affected.

Summary

27 patients had pulmonary decortications for various reasons. In each case the operation was successful.

In an unselected group of 10 cases lung function was measured, and was found to have improved strikingly in 9.

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Preliminary Communication

ATYPICAL HAPTOGLOBIN PATTERNS IN TUMOUR PATIENTS

USING starch-gel electrophoresis, Smithies [1] recognised three types of human sera. These types were later termed [2] 1–1, 2–1, and 2–2, and it became clear that the different protein components were the haptoglobins first studied by Jayle et al.[3] in Paris. Smithies and Walker [2] suggested that the three types were determined by a pair of allelic genes. In addition to these three types two modifications of the 2–1 heterozygote have been described. Giblett [4] described a 2–1 type having a much heavier concentration of haptoglobin in the region behind the β-globulin as well as in the fastest of the zones in the α-β region. Galatius-Jensen [5] described a 2–1 type with doubling of the fastest of the zones in the α-β region.

Fine and Creyssel [6] have investigated, by starch-gel electrophoresis, sera from patients with multiple myeloma, macroglobulinæmia, and atypical dysproteinæmia. They concluded that investigations of dysproteinæmias with starch-gel electrophoresis might be very rewarding.

In an electrophoretic examination of protein extracts from mouse rhabdosarcoma and normal mouse muscle, Miller et al.[7] have demonstrated seven major components in the tumour extracts and only three major components in the normal muscle extracts. Sorof and Cohen [8] found different electrophoretic patterns in proteins from rat hepatoma and normal rat liver. The electrophoretic patterns in human lymphoid tumours are similar to those of rat hepatoma and mouse rhabdosarcoma.[8]

The sera from 43 tumour patients and about two hundred patients with other diagnoses from the University and Tunasen Hospitals at Uppsala were investigated by starch-gel electrophoresis. Poulik's [9] discontinuous buffer system was used and hæmoglobin was added to the sera. Of the forty-three tumour patients eleven had unusual haptoglobin patterns, while the other two hundred patients

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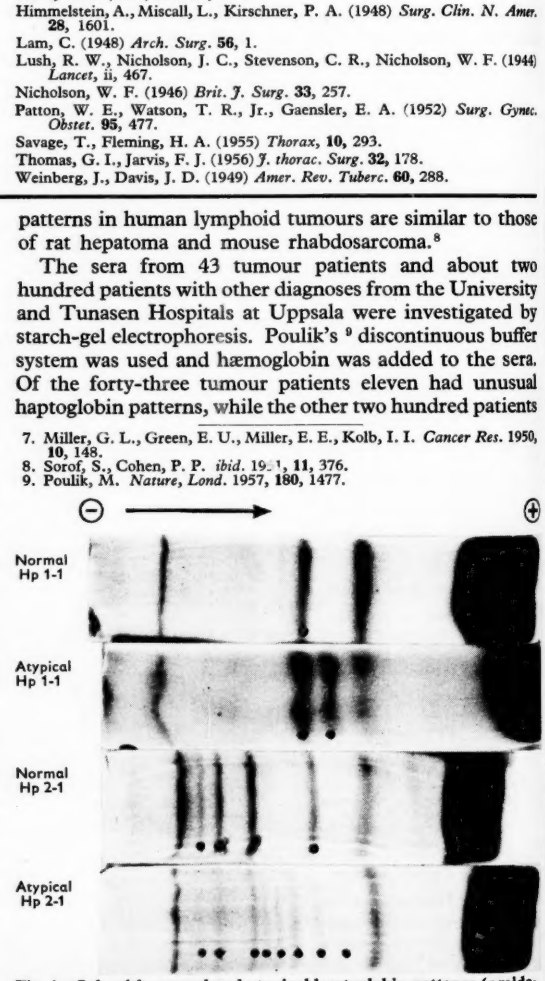

Fig. 1—Gels with normal and atypical haptoglobin patterns (amido-black-stained). Zones staining with benzidine indicated by black dots.

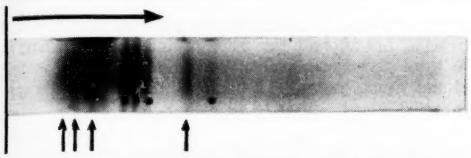

Fig. 2—Gel with atypical Hp 2-1 pattern (stained with benzidine). Normal zones indicated by arrows and extra zones by black dots.

revealed normal patterns. In three Hp 1–1 types a distinct doubling of the Hp-1 zone was observed, showing a fast-migrating benzidine-staining extra Hp-1 zone between the ordinary Hp-1 zone and the transferrin zone (fig. 1). In eight Hp 2–1 types the zone corresponding to the Hp 1–1 zone was also duplicated, and furthermore there were three extra benzidine-staining zones migrating faster than the fastest of the ordinary zones in the α-β region. The fact that the extra zones stain with benzidine makes it very likely that they belong to the haptoglobins (fig. 2).

No corresponding atypical variations of the Hp 2–2 type were observed. Thus the varying components may be the Hp-1 protein (cf. Allison [10]). The present findings seem to support Allison's hypothesis of the haptoglobin synthesis.

The distribution of the Hp-patterns in the forty-three tumour patients is shown in table I. In thirty-three patients the diagnosis was some form of cancer, while in

TABLE I—NORMAL AND ATYPICAL HAPTOGLOBIN PATTERNS IN 43 TUMOUR PATIENTS

Haptoglobin types						n
1–1		2–1		2–2		
N	A	N	A	N	A	
5	3	14	8	13	0	43

N=normal. A=atypical.

TABLE II—DIAGNOSES OF PATIENTS WITH ATYPICAL HAPTOGLOBIN PATTERNS

Diagnosis	Haptoglobin types	
	1–1	2–1
*Prostatic hyperplasia	1	1
Prostatic cancer	..	1
*Testicular hyperplasia	..	1
Testicular cancer	..	1
Pulmonary cancer	..	2
Cancer of uterine cervix	..	1
Breast cancer	..	1
Cancer of cæcum	1	..
Leukæmia	1	..

* Preoperative cases.

the other cases the type of the tumour was unknown. The diagnoses of patients with atypical patterns are shown in table II.

It was noted that the pattern was found only in fresh sera. In sera stored at −20°C for some weeks the pattern was rarely reproducible. However, fresh samples of blood from the same patients again showed distinct atypical patterns.

Like the previous electrophoretic data from protein extracts of tumour cells, the new atypical haptoglobin patterns in human tumour patients were characterised by an increase of fast-migrating protein components as compared to the pattern found in normal sera.

Further investigations are in progress. Full details of this work will be published elsewhere.

I thank Dr. H. Gedin, Biochemical Institute, University of Uppsala, for valuable technical advice.

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Reviews of Books

Cholera

R. POLLITZER (with two chapters written in collaboration with W. BURROWS and S. SWAROOP). *W.H.O. Monograph Series* no. 43. Geneva: World Health Organisation. 1959. Pp. 1019. £5. Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1.

A MAN stricken with cholera is a fearful sight and in its epidemic form no disease is more terrifying. It is true that we can now treat it successfully by replacing the fluid lost from the bowel, but it strikes most commonly where doctors and infusion fluids are equally scarce. Preventive vaccination is of some value but (as with vaccination against enteric fever) there is a dearth of reliable figures to guide us on the best vaccine or the best route of inoculation. If we no longer see the disease in Europe we must thank the sanitary engineers rather than our own profession, but who knows what is to limit its spread after a destructive war? As it is, it lingers in its oldest home in the delta of the Ganges and the Brahmaputra, and in spite of every human effort creeps out in epidemics which count their victims in tens of thousands. It is probably a safe guess (but only a guess) that most epidemics are spread by convalescent or symptomless patients, but from time to time (for example, in Egypt in 1947) major outbreaks arise whose origin remains a mystery. Indeed, in spite of its antiquity, cholera is a very mysterious disease, and Dr. Pollitzer has done a good service in assembling the facts about it in this book.

A good monograph is a noble work and this is a very good one. The reader who has digested every page may think that he knows it all, but he will know far less than the author who has read almost every word on this disease that has ever been written. If the book has a fault it is that there is too much of X and Y (who were not very critical workers and who have been dead these many years) and not enough of Dr. Pollitzer's own great experience and opinions. For example, after several pages on the standardisation of vaccines by their opacity he concludes with a warning that the methods are all unreliable. A lot of the work done on cholera has been ill-considered and it is pleasant to see how the genius of Robert Koch shines in these pages: not only did he describe the guilty organism but even his guesses on the epidemiology have been shown to be largely correct. But no-one should be too critical of the many authors quoted: there is a world of difference between deliberate research in a quiet laboratory and the attempts to discover reason and order among a panic-stricken population who are dying like flies. Dr. Pollitzer has had both experiences and it would have been interesting if he had speculated at greater length on the unsolved problems of bacteriology and epidemiology. His book should be in every medical library.

Surgical Treatment of Bone and Joint Tuberculosis

ROBERT ROAF, M.CH.ORTH., F.R.C.S., W. H. KIRKALDY-WILLIS, M.D., F.R.C.S.E., A. J. M. CATHRO, M.B. Edinburgh and London: E. & S. Livingstone. 1959. Pp. 137. 30*s*.

AT one time the treatment of orthopædic tuberculosis could very adequately be summed up in Owen Thomas's classic phrase " long, continued, and uninterrupted rest ": and yet a large number of bulky monographs were written on the subject. It is a measure of the extent to which antibiotics and chemotherapy have simplified the problem that today rest is regarded as no more than a valuable ancillary measure, and that a book of 137 pages can very adequately set out all a modern surgeon needs to know of the disease.

This volume is based on the experience of its authors when working at Oswestry and in East Africa, where bone and joint tuberculosis is still very common. So common, indeed, that many patients who, in this country would be admitted must be treated as outpatients or sent home after only a brief stay in hospital. Although two chapters are devoted to general considerations and to diagnosis, most of the book is based on an anatomical plan and deals with the disease as it is seen at

each of its common sites. The emphasis throughout is on operative treatment, and all the procedures suggested are fully described and amply illustrated.

Views on the best methods of managing surgical tuberculosis are still labile. Further trials of different techniques are urgently required, but many of these can henceforth take place only in the less developed countries of the world. Meanwhile, and particularly for surgeons working in such areas, this book is a reliable guide to present knowledge and to those techniques which hold most promise of success.

Hypertensive Disease: Diagnosis and Treatment

SIBLEY W. HOOBLER, M.D., associate professor of internal medicine, University of Michigan Medical School. New York: Hoeber-Harper. London: Pitman Medical Publishing Co. 1959. Pp. 353. 60*s*.

UNFORTUNATELY few physicians have the time or the opportunity to decide the relative merits of all the various drugs now available for the treatment of arterial hypertension, or to study closely the long-term effect of reducing blood-pressure in relatively mild and uncomplicated hypertension. Consequently they must refer to the experience of specialists, and this book by the director of the hypertension unit at the University of Michigan Hospital sets out to answer most of the questions in the management of hypertension. This practical book describes in much detail the drug regimes used by Dr. Hoobler as well as those used in other leading centres in the United States. Details of treatment are given in appendices. The treatment of every conceivable hypertensive complication or emergency has been covered, and sections are devoted to blood-pressure reduction in the presence of renal failure and cerebrovascular disease.

The differential diagnosis of secondary hypertension is considered in the first part of the book; but, since it is concerned solely with the management of hypertension, there is no discussion of the mechanism or pathogenesis of the primary type. None of the recommendations are particularly unorthodox, and the standard combination for severe hypertension (mecamylamine, chlorothiazide, and reserpine) is well known in this country. What is surprising is to learn that patients should record their own blood-pressures at home, but Dr. Hoobler is convinced of its value. He emphasises that the treatment of hypertension is an art as well as a science. Unfortunately the book was written shortly before the introduction of bretylium tosylate.

Proteins in Foods

Indian Council for Medical Research Special Report Series, No. 33. S. KUPPUSWAMY, M.SC., M. SRINIVASAN, D.SC., F.R.I.C., V. SUBRAHMANYAN, D.SC., F.R.I.C., F.N.I. Central Food Technological Research Institute, Mysore. New Delhi: Indian Council for Medical Research. 1958. Pp. 290. 12 rupees.

THIS book was instigated by the advisory committee on nutrition of the Indian Council for Medical Research, and the results justify the time and money which must have been spent on its production. A short but valuable introduction is followed by thirteen sections each devoted to one class of foodstuffs—e.g., cereals, legumes, milk, algæ, leaves, and grasses. All the sections contain two tables. The first gives the percentage of protein in the material, which is calculated by multiplying the total N by 6·25. This is not, however, the factor now accepted as the correct one for cereals and milk products. Figures for the biological value are also given, but those interested primarily in human nutrition should bear in mind that these assessments are nearly all based upon rat experiments. The second table gives figures for the "essential" aminoacids expressed as a percentage of the total protein. No new analyses have been made, but the book is a scholarly compilation of previous work. Hundreds of different materials and their derivatives are listed, with the original investigators responsible for the results.

The information is therefore rather specialised, but it is what is needed in India, Africa, and many other parts of the world where malnutrition, based upon protein and aminoacid deficiencies, has become the prior problem in nutrition, particularly for those responsible for the health of the weanling infant and young child. The book should have a wide appeal and a useful life.

An Introduction to Medical Genetics.

2nd ed. J. A. FRASER-ROBERTS, M.D., D.SC., F.R.C.P., director, clinical genetics research unit, Medical Research Council; hon. consultant in medical genetics, The Hospital for Sick Children, London. London: Oxford University Press. 1959. Pp. 263. 35*s*.

THE first edition appeared during the late war, and was at once recognised as a classic, because of the lucidity of the presentation and the thoroughness with which single-factor mendelian inheritance was explained. A unique feature was that all the examples and illustrations were of human conditions and not taken from organisms, familiar to the geneticist but not to the medical practitioner, such as the fruit-fly and the maize plant.

The second edition follows the same plan; new advances are incorporated and many new illustrations have been used. The blood-groups now have a chapter of their own, the section on multifactorial inheritance has been developed, and an important new chapter has been added on the science and art of advising parents on the genetic risks to their children.

The single-factor approach that Dr. Roberts uses is the logical one. But the disorders due essentially to single genes are, with the possible exception of essential hypertension, rare in this country and in most other parts of the world. The student will not, perhaps, meet a single patient with one of these disorders until he is a clerk in the children's wards. It will probably not be possible, therefore, to interest the more practically minded student in genetics until much more is known about the inheritance of common conditions; that is, until the section on the inheritance of common disorders in a book like this can come early, instead of near the end, and that may take a generation. But the student or practitioner who likes to delve deep for the first causes of disease will find genetics an enthralling subject, and Dr. Roberts' book the best starting-point in his studies. Further, he will be in a position to follow some of the most interesting developments in medicine in the next thirty years.

Peripheral Vascular Diseases

TRAVIS WINSOR, M.D., F.A.C.P., assistant clinical professor of medicine, University of Southern California School of Medicine, Los Angeles. Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959. Pp. 845. 125*s*.

PERIPHERAL vascular disease has recently migrated from the care of the physicians to the intervention of the surgeons, and contemporary textbooks tend to be dominated not by physiology or clinical science but by surgical techniques. Dr. Winsor is a physician in the traditional mould of Thomas Lewis: almost half his book deals with the applied physiology of the sympathetic nervous system and the vessels, introducing both the relevant physics and recording techniques. Vascular diseases are briefly rather than extensively discussed, and the emphasis hangs on medical rather than surgical problems: treatment is similarly oriented. One refreshing feature is the profusion of black-and-white diagrams which form an excellent basis for undergraduate teaching: indeed, it is probably to the student or the early postgraduate that this monograph will appeal most.

Psychology, The Nurse and The Patient (5th. ed. London: *Nursing Mirror* Books, Iliffe & Sons. 1959. Pp. 200. 15*s*.)—This popular and practical little book by Dr. Doris Odlum has been revised and brought up to date. The chapter on the nursing of children now emphasises the importance of avoiding as far as possible the separation of young children from their mothers. A final chapter outlines the changes to be introduced by the new Mental Health Act.

THE LANCET

LONDON 28 NOVEMBER 1959

Fibrocystic Disease of the Pancreas

AFTER a series of metamorphoses in the first twenty-five years of its recognition as a separate entity,[1] fibrocystic disease of the pancreas continues to challenge, surprise, and exasperate its devotees. A few clinicians still believe that the primary defect lies in the pancreas. Lack of pancreatic juices, it has been argued, can cause severe deficiency states, and vitamin-A deficiency in particular; and this could lead to secondary changes in the bronchial epithelium, the skin, the liver, and other organs.[2] The chief weakness of this hypothesis is that, though vitamin-A deficiency is probably common enough in patients with fibrocystic disease (and may contribute to their susceptibility to infection), the pancreatic component of the syndrome is often mild and late compared with its supposedly secondary effects.[3–7]

Clinical experience and laboratory observations rather suggest a widespread disease with focal manifestations. Soon after the illness had been clinically identified several hypotheses were put forward (they range from transplacental infection and Rh-immunisation to dietary deficiencies [8–10]), but cast into temporary limbo for lack of supporting evidence. In 1943 FARBER[11] made the ingenious suggestion that the syndrome could be a systemic disease of mucous glands—a concept later expanded to include a " series of exocrine glands ".[2 12] Such " mucoviscidosis " or " mucosis " could account for most of the disparate features of the syndrome as they were then known—for the digestive triad of steatorrhœa, meconium ileus, and biliary cirrhosis as well as for the pulmonary lesions. Though no anatomical fault could be demonstrated in the mucous glands,[13 14] FARBER'S hypothesis remained—and still remains—capable of several interpretations. Stimulated by the work of PAULING'S group, INGRAM and others,[15–17] who think in terms of " molecular diseases ", now look on mucoviscidosis as expressing a structural error in a mucoprotein, similar to the molecular flaw in hæmoglobin which gives rise to the hæmoglobinopathies. Others ascribe it to a specific deficiency of a proteolytic enzyme: this could result in the defective breakdown of mucus and in the formation of those tenacious plugs in the pancreatic, salivary, bile, and other excretory ducts which are such a striking feature of the disease, Unfortunately mucus remains the most enigmatic of body secretions: from among its constituents (at least three different mucoproteins and several polysaccharides) we have not even selected yet the likeliest candidate for the molecular defect or the probable subject of defective enzymatic breakdown.[18 19] But if the case against mucus is hard to prove, it is no less hard to disprove. In his useful list of guiding facts Dr ROBERTS (whose article appears on p. 964 of this issue) contends that the mucus of mucoviscidosis is biochemically normal; but, though we welcome a reminder that no chemical abnormality has been demonstrated in it (especially after ambiguous statements suggesting that its increased viscosity and abnormal histological appearance imply a chemical structural deviation from the normal), it is too early yet to give the chemical all-clear. We doubt whether with the methods hitherto used it would be possible to pinpoint minute deviations from the normal in the molecular structure of all the protein molecules, such as we now know can cause serious disease. The prima-facie difficulty of fitting the abnormal loss of sweat-electrolytes into the original picture may weigh more heavily against " mucoviscidosis ".

This remarkable aspect of the syndrome first attracted attention in the 1948 New York heat-wave, when children with known fibrocystic disease were admitted to hospital in a state of severe salt-depletion.[19] After excessive urinary salt-loss had been excluded, the cause was found to be threefold to fourfold increase in the electrolyte-content of the sweat. This finding later became the basis of more or less elaborate " sweat tests ", useful not only for screening of suspected mild cases but in genetic studies of clinically silent carriers.[20–24]

The mechanism of the sweat abnormality is obscure, but it has given Dr. ROBERTS a lead in evolving his ætiological hypothesis. A paradoxical nerve-supply by cholinergic fibres which anatomically are part of the sympathetic system links sweat-glands to such topographically remote organs as the pancreas, Brunner's glands, and the bronchial epithelium. Overstimulation of these tissues, followed by exhaustion (not necessarily irreversible), could well be at the root of fibrocystic disease—a possibility the more attractive since it offers hope that effective treatment might be round the corner. But it still needs factual support.

The venerable dispute of humoral *versus* nervous control of pancreatic secretion (the list of disputants reads like a roll-call of a physiologists' *Burke's Peerage* [25–32])

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is veering back to PAVLOV's original view [27]: it seems that in normal pancreatic digestion nervous impulses play a part very subordinate to secretin and perhaps other gastrointestinal hormones. Admittedly under experimental conditions stimulation of the peripheral end of the cut vagus leads to a flow of thick, concentrated pancreatic juice; but how faithfully parasympathicomimetic drugs, such as pilocarpine, reproduce this effect is not clear.[33 34] Nor are we certain about the presence and function of vagal inhibitory fibres.[30] THOMAS [35 36] has reiterated his view that the hormonal and humoral controls are closely linked (able to act both synergistically and antagonistically) and possibly both release a common final chemical intermediary. In addition to its vagal supply the dog's pancreas is supplied with sympathetic fibres; and, curiously, their direct tetanisation provokes a flow which resembles that induced by vagal stimulation.[37] This practically refutes one of FARBER'S [38] later suggestions—that fibrocystic disease may reflect a sympathetic-parasympathetic imbalance. But, since these splanchnic fibres behave as if they were cholinergic (their effect being abolished by atropine), the similarity does not contradict ROBERTS' hypothesis. Surprisingly little attention has been paid, however, to afferent autonomic nerves: no less than 90% of the cat's vagus nerves are " sensory "; and their role in transmitting reflex impulses may be of prime importance.[39 40] We are even more ignorant of the factors which govern the elaboration (as opposed to the secretion) of pancreatic juice: they almost certainly include vascular, endocrine, and nervous influences.[41 42]

With little help from physiologists, some will be attracted by ROBERTS' inverse analogy between his hypothesis of the ætiology of fibrocystic disease and the ætiology of myasthenia gravis. Others may be reminded of the exacting shopper whom GERALD DU MAURIER depicted as she turned to the exhausted assistant: " Now we're getting somewhere at last! This is the exact opposite to what I want." It is not impossible that the wards will provide proof of Dr. ROBERTS' acetylcholine hypothesis before this receives the laboratory's sanction.

New approaches to fibrocystic disease are certainly needed. That the condition is by no means rare is now underlined not only by calculations based on family studies [23 24 43–45] but also by clinical and public-health surveys: SIRKEN et al.[46] report from the United States that in a nationwide survey they found that in one year 2500 patients either died or were discharged from hospital with this diagnosis—a 50% increase in five years. We are gradually realising that the syndrome may not become clinically manifest till adolescence or even adult life; and that the spectrum of presenting features is far wider than had been thought [6 19 45]: they now include jaundice of the newborn, non-allergic asthma, sinusitis, Kartagener's syndrome, portal hypertension (with hæmatemesis), hypersplenism, and even myocardial disease.[23 24 45 47–49]

New Sources of Protein

THE people of Britain have probably never been so well fed as they are today.[50] In the United States the disposal of surplus wheat presents a real economic difficulty, and stocks are now as high as 35 million tons.[51] By contrast in Africa, Asia, and Latin America hundreds of millions of people are unable to get enough food to meet their physiological needs. Professor BROCK in his Humphry Davy Rolleston lectures, the second of which appears in this issue, contrasts the diseases that the clinician interested in nutrition sees in different parts of the world. In prosperous countries the important nutritional diseases are obesity and ischæmic heart-disease, which are associated with dietary excesses. In the underdeveloped parts of the world deficiency diseases remain all too common.

Kwashiorkor, attributable to insufficiency of suitable dietary protein, is, as BROCK emphasises, the most widespread and important deficiency disease in the world today. Protein requirements are relatively greatest in the first years of life, when the child is growing rapidly; evidence of protein deficiency is commonest soon after the child has been weaned. Clinicians are now, for the most part, well aware of the acute manifestation of the disease and of the methods of treatment based on the use of skimmed milk or other good sources of protein or equivalent mixtures of aminoacids. But for every child with kwashiorkor so seriously ill as to need admission to hospital, there are probably at least a hundred whose development, both physical and mental, has been impaired at a critical period of life by the disease. The long-term effects of insufficiency of protein in the diet during the early critical years are still not widely enough appreciated—especially by those responsible for planning for the health and development of agricultural communities in the tropics. Mental lethargy is constantly present and usually severe in all children who are seriously ill with the disease.[52] In countries where kwashiorkor is common, inadequate dietary protein can reasonably be supposed to cause widespread slowing of mental development. Many educationists do not seem to have appreciated this.

In prosperous countries, foods of animal origin normally supply a considerable proportion of the protein in the diet. Cattle and sheep can be regarded as apparatus for concentrating the protein which is present in low concentrations in grass and other vegetable material. This apparatus is effective but not very efficient; for the total nutrients, including protein, that become available to man from land used for pasture is much less than would be available from the same land under the plough.

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50. See *Lancet*, Nov. 7, 1959, p. 798.
51. See *ibid.* Oct. 10, 1959, p. 572.
52. Gerber, M., Dean, R. F. A. *Courrier*, 1956, **6**, 3.

In many areas where kwashiorkor is common, there is not the land available for extensive animal husbandry; and where, as in parts of Africa, land is available it will take many years to build up large enough herds to contribute significantly to the food-supply. In many countries, it is quite unrealistic to suggest that improvements in animal husbandry could make good in the foreseeable future the existing deficiencies in the supply of protein.

Additional sources must be found from vegetables. Formerly vegetable proteins were classified as second-class and regarded as inferior to first-class proteins of animal origin; but this distinction has now been generally discarded. Certainly some vegetable proteins, if fed as the *sole* source of protein, are of relatively low value for promoting growth; but many field trials have shown that the proteins provided by suitable *mixtures* of vegetable origin enable children to grow no less well than children provided with milk and other animal proteins. WIDDOWSON and MCCANCE's [53] work in German orphanages showed that children could grow well and remain in excellent health without milk, provided they received a diet containing a good mixture of vegetable proteins.

Additional sources of protein are particularly necessary for communities whose staple food is either a cereal or a starchy root. Where there is little or no animal husbandry, this additional protein must be of vegetable origin. Soya beans are rich in protein and have been used by the Chinese for generations, but they have never become very popular with either agriculturists or consumers elsewhere. In many parts of the tropics groundnuts are grown as a cash crop for the oil. The cake that is left after the oil has been expressed is rich in protein and well known as a valuable cattle-food. SUBRAHMANYAN and his colleagues in India have shown that groundnut protein can be incorporated in a vegetable milk [54] and also in a " multipurpose " food.[55] Field trials have shown that these are acceptable, and their cost is not very great. LADELL and PHILLIPS [56] have found that cassava flour can be enriched with groundnut protein, and the product is acceptable to Nigerians.

More revolutionary is the demonstration, recorded by Mr. PIRIE in this issue, that leaves can provide proteins valuable as human foods. So far, leaf protein seems to have been tested only in this country and on a very small scale. It is apparently a nutritious, if somewhat unexciting, food. We hope that PIRIE's offer to send lots of up to 50 kg. of this new protein to any part of the world for field trials will find many acceptors.

Leaf protein may become a major weapon in the battle against kwashiorkor. The raw material is readily available in most parts of the world, and cultivation costs nothing. The setting up of small extraction plants locally should not prove either difficult or expensive. The real problem is likely to be in persuading the mothers of the value of a new and strange food for their children. As PIRIE points out, there are many ways in which leaf protein could be incorporated in a diet: the discovery of the way most acceptable to a particular community is a matter for local research. If the seriousness of kwashiorkor both in its acute and in its chronic forms can be appreciated, then the necessary enthusiasm for preventive measures will follow. Encouragement for such projects can be found in a report,[57] submitted to the Committee on Foreign Relations of the United States Senate, which emphasises the importance of new sources of protein. PIRIE's work on the separation of leaf proteins is described, with the comment: "unless a social mechanism can be created to introduce the simple machinery where it is needed, it will remain where it is—a curiosity to Britons, an unknown potential to areas where it could be tried, tested, and adapted to local circumstances ". This surely is a challenge to men of good will and ingenuity in Africa, in Asia, and in Latin America.

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Annotations

PSYCHROPHILIC BACTERIA

BACTERIA are not easily discouraged, and it is simpler to list the very few environments which are without them than to name each of the many in which they are found. Ice-boxes and refrigerators are now widely used to preserve food and bottles of blood from the effects of bacterial growth. Sometimes the prevailing temperature (0–4°C) fails to restrain the bacteria, with resultant spoilage of the food or transfusion of contaminated and highly toxic blood.[58] Such accidents are happily rare; but consequently little attention has been given to the bacteria which grow in the cold—the psychrophils. We are more interested in the mesophils, which include the bacteria commonly parasitic on man, and the thermophils, which operate in our compost heaps and present problems to the food-canning industry because some of them have spores with exceptional resistance to heat.

We should take more account of the psychrophils because of their interesting biological attributes, and because the increasing use of cold storage—in the collection of milk in large cooled tankers, for example—will inevitably increase the number of times when the low temperature fails to accomplish its desired object.

In the past, as Ingraham and Stokes [59] emphasise in an informative review, psychrophils have often been defined in terms of optimum growth temperature. But the temperature ranges chosen have been set either so low as to include virtually no known bacteria or so close to that of the mesophils as to fail to separate the two groups. Their own definition usefully distinguishes the psychrophils as the group of bacteria which grow appreciably and often abundantly at 0°C within two weeks. The optimum growth temperatures—a very different matter—mostly lie in the range of 20–40°C, but they often grow with considerable speed if the temperature rises to 4°C. Thus defined, psychrophils are widely distributed in soil, air, fresh and salt water, and milk and foods. Most of them belong to the genus Pseudomonas. In much smaller

57. Possible Non-military Scientific Developments and their Potential Impact on Foreign Policy Problems of the United States. United States Government Printing Office, Washington, 1959, no. 45,633.
58. McEntegart, M. G. *Lancet*, 1956, ii, 909.
59. Ingraham, J. L., Stokes, J. L. *Bact. Rev.* 1959, **23**, 97.

numbers they may be found in the genera Achromobacter, Flavobacterium, Alcaligenes, Micrococcus, and a few others. Psychrophils are often luminous; they may be responsible, for example, for the glowing light which may be seen surrounding fresh fish in a dark pantry. Unfortunately this striking appearance is not very familiar nowadays because fish is rather slow in reaching the urban household and the psychrophils on the surface of fish are fairly soon outgrown by non-luminous organisms which are also abundant in that situation. At any rate, the cheerful glow surrounding the fish is emphatically not a cause for rejecting them—as cautious housewives (not from Aberdeen, where they know fish and esteem money) have been known to do.

Besides glowing, psychrophils may synthesise green, yellow, orange, red, and other pigments. They also ferment carbohydrates, decompose proteins, produce indole, and reduce nitrates; in short, they behave like other bacteria but go more slowly about their business. The dangers they may cause in blood-banks have already been stressed [58]; elsewhere they are mainly of importance to the food and dairy industries, especially because they may grow rather quickly if transferred from temperatures at or below 0°C to domestic refrigerators at about 4°C. In such circumstances the spoiled food may quickly show the presence of pigment or acquire an unpleasant smell or taste. Attempts to restrain these undesirable events by adding antibiotics to the food have shown that antibiotic-resistant strains of psychrophils are not slow to emerge. The fundamental mechanism which enables psychrophils to grow at low temperatures remains unknown.

CLINICAL STAGING FOR BREAST CANCER

CANCER statistics are a potent source of misunderstanding, and even ill-will, through failure to recognise common standards. To take one example, survival: should this be estimated from the onset of symptoms, first attendance (at the doctor's surgery, or the hospital?), or first treatment? In this country survival is usually dated from the moment treatment was instituted; but this practice is by no means universal, and reports seldom specify the convention that has been followed. A further cause of disparity is the omission by some of untreated cases from survival statistics. It is good news, therefore, that one important aspect has at last been agreed internationally.

Efficacy of treatment can be judged in relation to two factors—the degree of malignancy and the extent of spread. Broders' classification is the classical example of an attempt to assess the degree of malignancy; but it cannot be applied to every case since biopsy material may not be obtained. Clinical staging is suitable for defining the extent of the growth in those sites where the primary lesion and its areas of spread are readily revealed either clinically or radiographically. Thus, whereas stomach cancer can be "staged" only in cases submitted to laparotomy, the extent of breast cancer can be assessed in all cases even without operation. It is true that histological examination may not always support the clinical assessment, since involved glands may have been impalpable; but this matters little since treatment is selected in the light of the clinical, and not the pathological, findings; it is better, therefore, that results be evaluated against this yardstick.

International agreement has now been obtained on a system of staging, to be applied from the beginning of next year. The system, chosen by the Union Internationale Contre le Cancer, is the "T.N.M.": T refers to tumour, N to nodes, and M to metastases, each initial being followed by a numeral to indicate size, fixity, or extent. Conversion to this notation from other systems is not difficult; and it has the merit that histological classification can be incorporated—which may mitigate errors due to observer variation. The purpose of this international effort is not only to assess the practicability of "staging" in universal practice but also to find out whether the interests of both radiotherapy and surgery can be served by one system.

Copies of the report setting out the method may be obtained from Dr. P. F. Denoix, Institut Gustave Roussey, Villejuif, Seine, France.

TUBERCULOSIS ERADICATION?

THE tuberculosis situation in Denmark, a country of $4^1/_2$ million people, has been reviewed by Groth-Petersen et al.[1] Such reviews are of more than local interest, because changing circumstances may require a change of emphasis in anti-tuberculosis work in many countries.

Over the past thirty years tuberculosis has occupied much the same position in Denmark as in Britain except that there most indices are rather lower. Many workers outside Denmark believe that in that country B.C.G. has long been used extensively; but in fact its widespread use is a post-war development. The decline in mortality (rapid since 1947), the rather slower decline in morbidity, and the probably very low rates of infection in children are all essentially similar in Denmark and this country. The age and sex distribution of mortality is also very similar, though the peak of mortality in older males is rather more pronounced in Britain.

In 1950–52 an organisation known as the Danish Tuberculosis Index was set up as a cooperative undertaking of the National Health Service of Denmark and the W.H.O. Tuberculosis Research Office. Under the technical direction of this organisation, a mass campaign was carried out in 1950–52 covering particularly the age-groups 1–6 years and 15–34 years. All in these age-groups were offered a tuberculin test with B.C.G. vaccination for the negative reactors. A 35 mm. chest X-ray was carried out at the same time on those aged 15 years and over. Children of school age (7–14 years) were not included, because since 1949 they have been included in the school scheme of tuberculin testing and vaccination. From this campaign very full records were compiled and held in a central office for the whole country. The essential features of this record consisted of:

(1) The mass campaign roster, including a card for every person in the age-groups 1–6 and 15–34 years whether they attended the mass campaign or not.

(2) A vaccination file of cards for persons of 15 years of age or more at the time of the campaign who had a record of having been vaccinated before the campaign.

(3) A tuberculosis case register consisting of cards for all cases of pulmonary tuberculosis reported since 1937, all cases of extrapulmonary tuberculosis reported since 1951, and cases of pulmonary tuberculosis notified between 1920 and 1936 for which a card could be found in the mass campaign roster.

From the results of the campaign in 1950–52 those attending for examination were divided into subgroups according to the result of a single chest radiograph and a single tuberculin test. All cases of tuberculosis in the $3^1/_2$–4 years after the campaign were matched against the central register held by the Danish Tuberculosis Index; and thereby the risks of tuberculosis developing in these subgroups could be estimated.

1. Groth-Petersen, E., Knudsen, J., Wilbek, E. *Bull. Wld Hlth Org.* 1995. **21**, 5.

With regard to the X-ray examination, it was found that the risk of tuberculosis in those passed as completely normal by both readers of the miniature film was extremely small; this group formed about 90% of the adult population but contributed less than two-thirds of the cases. Those with radiographic evidence of healed lesions formed about 7% of the population and ran about twice as great a risk of developing active tuberculosis as those with normal films. The remaining 3% were classified as having suspicious findings; and this group had the highest incidence of subsequent tuberculosis—fourteen times as great as in those with normal chest X-rays. As previous work has shown, the risk of developing tuberculosis is greater in young adults than in older adults, and this trend was evident in each of the three groups.

Classification of the apparently healthy population at the time of the survey by the tuberculin-test results showed very low attack-rates in those tuberculin-negative and in those vaccinated with B.C.G. Most of the subsequent cases of tuberculosis were in persons positive to tuberculin at the time of the test. Within this group of positives there was in young adults a considerable variation in risk according to the level of sensitivity. Generally speaking, the higher the sensitivity the greater the likelihood of subsequent tuberculosis. For all age-groups, the risk of tuberculosis in those with 6–12 mm. reaction to the 10 tuberculin-unit test was low.

On the basis of these results, Groth-Petersen et al. suggest that some changes should be made in traditional methods of tuberculosis control in Denmark. Routine X-raying of children has already been abolished (in some counties routine B.C.G. vaccination of infants and children is to be abolished or at least postponed until the last year of school). Perhaps the most important recommendation is that persons in the older age-groups with normal findings on a single chest radiograph, whether full-size or miniature, need not be called back for further examinations; but the important corollary of this is that persons of any age with suspicious X-ray lesions, and all young people with large tuberculin reactions, should be systematically followed up. (This recommendation needs to be taken in association with the statement that the films were intentionally " over-read ".) In Denmark these high-risk groups with suspicious X-ray shadowings and high levels of tuberculin sensitivity can be kept under close and continuous supervision, and can perhaps be given anti-tuberculosis drugs prophylactically.

Most of the recommendations conform with practice in many centres in Britain. What is perhaps not yet fully enough appreciated here is the need for long-continued close supervision of even minor abnormalities or doubtful abnormalities. A considerable part of the tuberculosis of the future will arise in patients with very slight radiographic variations from the normal—that is, in patients with dormant infections. Many members of the chest service are turning to the management of diseases other than tuberculosis; but they should not lose sight of the fact that there is a very large reservoir of persons with minor radiographic abnormality among whom a fair amount of frank tuberculosis is going to develop. These will require much attention at chest clinics for many years to come.

In this country a central register of tuberculous persons would probably be unmanageable at present, because of the numbers; there is little point in keeping a register for each of the hospital regions in view of people's mobility in this country, though such registers might be more useful than those kept at present for the local-health-authority areas or chest-clinic areas. A start might be made, however, with a national register of persistently sputum-positive cases; any patient who has a positive sputum in two consecutive years is a potential menace and a risk for the future, since patients with sensitive organisms become sputum-negative with less than a year's treatment.[2] As the number persistently sputum-positive declines the register might be extended to include all with tuberculosis.

MEDICAL EDUCATION OF THE PUBLIC

IF he had been able to foresee that his lines about " a little learning " being " a dang'rous thing " were to become the most frequently misquoted passage in English literature, Alexander Pope would probably have derived a certain satirical satisfaction. For all those who misrepresent him so exactly prove his point. Learning is not synonymous with knowing, and knowledge itself can never be other than advantageous. The motion discussed by the Hunterian Society on Nov. 16 declared provocatively " that education of the public in medical matters is to be deprecated ", and a witty and spirited debate ensued.

The audience was reminded by Dr. Richard Asher that what the public liked was not always what was good for them. At one time they had enjoyed public executions. And nowadays, he felt, appendicectomy on television had become a substitute for capitectomy in the market place. It made no difference that the educators were often well-meaning. A doctor who read a medical feature in a popular magazine might feel it had been very wisely worded by a colleague, but unfortunately the fact that an article was well written was no guarantee that it would be well comprehended. Dr. Asher particularly deplored the " sob-stuff stories ", such as those which reported how Teresa Teardrop had been given her chance of health by the joint contributions of her neighbours; the sensational " digest " features which enthused over the hope that an extract from the blood of sleeping dormice held out to insomnia sufferers (without mention of the value of simpler remedies); and the idolaters who built up the concept of the super-specialist in the layman's mind, to the detriment of the general practitioner. For himself, Dr. Asher said, he would like to see the medical profession more revered by the public. A proper spirit was typified by the *Punch* cartoon of a patient in a casualty department tearing off the shroud which has been thrown over him and protesting " I *ain't* dead, Doctor ": at which an attendant presses him back with the firm assurance " Lie down, the doctor knows best ".

Opposing popular medical education on different grounds Mr. Guy Warrack believed there was still an element of magic in medicine—a magic which depended on suggestion and which was often embodied in a bottle of medicine. Doctors, he felt, often prescribed remedies with less doubt about their psychological efficacy than about their physiological properties. Take away this magic and the public might well turn to patent medicines and seek it there. Not of course that gullibility was the only essential for a cure. The best results were forthcoming if a remedy required some effort on the patient's part, such as that entailed by the collection of toad's spittle on St. John's Eve. The doctor too must play a confident role. The shortcomings of one of the most famous physicians of all constituted an object lesson in how not to behave. When Dr. John H. Watson was asked in 1888 by Holmes " What do you know, pray, of Tapanuli fever or the Black Formosa Corruption ?", instead of mak-

2. Crofton, J. *Brit. med. J.* 1959, i, 1610.

ing some noncommittal reply he said " I have never heard of either ". It was not surprising that two years later we found him admitting " I have nothing to do today ", or that in 1892 he described his practice as " quiet ". By 1895 he had been constrained to sell it up altogether.

Nowadays, protested Dr. Harvey Flack, editor of *Family Doctor*, the face of medicine had so changed that it could no longer be regarded as a mystery, and a more literate and intelligent public was demanding information. True, people were not always sensible and rational in their demands. His office had received more than one postcard from a mother worried about her baby, even though it was gaining weight and doing well, because a nurse had been heard to say " The baby has an umbilicus". When his journal prefaced an article on a public analyst by the story of his exposure of ridiculous claims for the medicinal properties of peppermint water sold under an imposing label, scores of readers wrote asking where they might obtain the preparation. But a real demand for information now existed. Was the profession going to opt out of the responsibility it should properly bear?

Supporting Dr. Flack, Mr. Wynford Vaughan-Thomas, the well-known broadcaster, also pleaded for the instruction of the layman. The doctor must have cooperation from his patients and he would obtain more from a properly informed and instructed individual. A vote then indicated that in the view of the audience the original motion had been upheld. It is a little surprising that before the proceedings closed no-one had fallen into error over the poetry of the " wicked wasp of Twickenham " who was only $4^1/_2$ feet tall. But no-one had remembered, either, that he also wrote " The proper study of mankind is man ".

PRECORDIAL CATCH

In one of his stimulating Lettsomian lectures earlier this year Dr. Asher [1] drew attention to a chest pain which as far as he knew had not been described in any published report and which bore no name. It now transpires [2 3] that this pain was described by Miller and Texidor in 1955 [4] under the title " precordial catch "; and these workers have reported a further 28 cases.[5]

The pain is invariably sharp and sudden, usually at or near the cardiac apex, but sometimes on the right side. Characteristically it is shortlived, lasting at the most a few minutes; attacks may recur every few hours, but commonly months or years separate each episode. The precordial catch is usually felt at rest in the sitting position or when the sufferer is " bent over ": its effect is to cause shallow breathing, but forced deep inspiration, though painful, often brings relief. The name, derived from the catching sensation described by some patients, implies no knowledge of the cause. So far none has been found, and the symptom is usually experienced by apparently healthy adults—especially men.

The precordial catch is clearly benign; but the nervous may suspect heart-disease, and recognition is important in order to differentiate it from other types of chest pain so that the patient can be reassured. Why this symptom has not been described before is uncertain: as Asher has shown, it is certainly not uncommon—over a third of his audience at the Medical Society of London admitted personal experience of it. Asher believes that it has escaped attention because, though acute, it is unharrowing and unassociated with angor animi; and another reason may be that it is so shortlived. Patients seldom complain unless a symptom recurs, or unless they are anxious. Now that this symptom has a name, we may discuss it freely and perhaps someone will discover the cause.

1. Asher, R. *Lancet*, Sept. 19, 1959, p. 359.
2. Oski, F. *ibid.* Oct. 24, 1959, p. 677.
3. Asher, R. *ibid.* Oct. 31, 1959, p. 735.
4. Miller, A. J., Texidor, T. A. *J. Amer. med. Ass.* 1955, **159**, 1364.
5. Miller, A. J., Texidor, T. A. *Ann. intern. Med.* 1959, **51**, 461.

RISKS OF PROGRESS

The hazards of scientific progress were considered by Lord Adrian in a Fawley Foundation lecture delivered at the University of Southampton on Nov. 17. In the 19th century and the earlier years of the 20th century, the progress of technology caused few misgivings, because the results were generally acceptable. In this period physical strain and discomfort were reduced, and transport and communication improved. Technology and industry, Lord Adrian said, could still advance along this line, for many parts of the world had yet to be freed from poverty and hard labour—though " the attack may end in confusion if the timing of the different movements has not been adequately supervised, if they allow the population of the world to increase more rapidly than we can increase our machinery for feeding and housing it, and if we exhaust our stores of metals and coal and oil before we have learnt how to fuse the hydrogen atom ". But supposing that all went well, and that the increasing control over the material world soon gave all its inhabitants the means of satisfying their primary needs, secondary needs would grow in importance and offer new fields for industry: the television sets and supplies of ice-cream which were luxuries to one generation were almost necessities to the next. Developing and satisfying secondary needs might bring increased danger—of injury, disease, or genetic deterioration.

The basic issue was whether we should aim at living safely rather than dangerously, but we had no agreed scale of values. Two postulates seemed to carry weight—first, that the risk of serious disease was of greater concern than the risk of injury, and secondly that the human race should remain at least as healthy and intelligent as at present. Lord Adrian balanced actual gain against possible loss in the applications of nuclear energy and radiation, and went on to declare that industry would aim at developments which would expose us to changes in the air we breathed, the food we ate, the clothing we wore, the temperature and humidity of our rooms, and the amount and kind of physical exercise we took. This being so, we must encourage research in genetics and medical science in general, and in particular we must develop the services which plotted the incidence of disease of all kinds. " Without repeated health surveys we shall never be rid of the fear that our progress is making the world a more dangerous place to live in."

This, however, was not the only fear to be considered. If we set out to save the unfit we must expect more unfitness in the world and more inheritance of the factors which promoted unfitness. But, Lord Adrian observed, doubling the mutation-rate would not double the load of inherited weakness until many generations had elapsed, for many of the faulty genes would be recessive or sex-linked. Much the same view was expressed by Prof. P. B. Medawar in his second Reith lecture on Nov. 21.[1] Less, he said, was to be feared from preserving the genetically ill-favoured than from a slow decline in human intelligence which, if it was happening at all, was due to the relatively greater biological fitness of the rather stupid.

Dr. G. F. Abercrombie has been elected president of the College of General Practitioners.

1. See *Times*, Nov. 23, 1959.

Special Articles

LEAF PROTEIN AS HUMAN FOOD

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PAST food shortages are indisputable; there is less unanimity about present-day shortages, partly because their recognition would often tend to indict some government, or system of government. Nevertheless the Food and Agriculture Organisation maintains that there are at present 1800 million hungry people.[1] No-one disputes that, in spite of existing shortages, the population of the world is increasing by 40–50 million a year. This rate may well be exceeded when hygiene and medical services diffuse more widely. Ultimately, no doubt, contraception will bring the increase under control, but that cannot happen quickly. An increasing demand for food is therefore likely to be with us for many decades.

Vigorous attempts are being made, along conventional lines, to meet this demand. More land is being brought into cultivation, and the land is getting more fertiliser and drainage or irrigation; crop varieties are being improved and pests and diseases limited. All this is immensely important and will go far towards meeting the immediate demand, but it is reasonable to doubt if it will go the whole way. Furthermore, those foodstuffs that are easiest to produce tend to contain a smaller percentage of protein than is needed in a balanced diet; there will probably be a continuing protein deficiency even if agricultural developments along conventional lines produce an adequate supply of calories. In some countries, animal products with a higher ratio of protein to calories are used to redress the balance in spite of the animal's inefficiency as a converter.[2] But, as the demand for food increases, we must expect the number of animals kept to diminish—as in war-time Britain, the land will be needed to grow crops that people can eat directly without conversion in an animal. The importance of animal products in the diets of those who live in the more highly developed countries may therefore be expected to diminish, and it is unlikely that animal protein will solve the problem for those in under-developed regions—that is to say, for the bulk of humanity. As in South-East Asia today, animal products are likely to slip generally more into the role of condiments than of foods. Fish could be used more extensively, and so could legume seeds and high-quality leafy vegetables; but it still seems prudent to look carefully for further extensive sources of protein to satisfy existing and future needs.

THE PROCESS

All the protein that is eaten as animal products, seeds, or tubers was made initially in the leaves of plants, and the presence of protein in leaves has been known since 1773 when Rouelle separated *la matière glutineuse ou végéto animale* from hemlock. The importance of leaf proteins in the biochemical processes of plants was recognised at the beginning of the century, and preparations have been made during the past fifty years from a great many different species; but, in spite of vigorous advocacy by Ereky and Slade, no attempts at large-scale separation were made until 1940. Since then machinery for the extraction has been gradually evolved [3 4]; it is still being improved. With the unit at Rothamsted it is already possible to make 100 lb. of protein a day. Little general interest was at first taken in attempts to make leaf protein, and there was even some official hostility to the work; but in the past few years interest has been growing and several commercial units for making leaf protein have been advertised. This spreading of interest is very welcome because it is only by making use of the good aspects from many processes that the best will be found. But caution is necessary; some of the arrangements that have been proposed seem to be insufficiently flexible to cope with a raw material with the wide variations in texture and water content found in leaves, while others may be too intricate to give a cheap product or insufficiently robust to stand up to the stones and similar objects that must be expected occasionally in an agricultural raw material. These are points that can be discovered by a reasonably prolonged trial.

In essence the process of extraction is simple. Fresh green leaves are pulped, and the juice is pressed out and strained to remove residual fibre; it is then heated to 80°C and the coagulated protein is filtered off, resuspended in water, and filtered off again. This washing process can be repeated if the original leaf was strongly flavoured. The final product is a dark green cake with little or no smell or taste. It contains 60% of water—i.e., it has the consistency of cheese or yeast—and keeps at room temperature for a week or so, but then slowly grows moulds. It keeps indefinitely in deep-freeze and can be canned. Direct drying in an oven or air stream generally gives a rather hard granular product; this hardening can be avoided by drying in the presence of flour or some other materials or by freeze-drying.

THE PRODUCT AND STARTING-MATERIAL

So far, leaf protein has been spoken of as if it were a definite entity, but it is in fact a mixture of an immense number of different proteins. This is advantageous because it is likely that a deficiency of any aminoacid in one protein will be compensated for by the other proteins so that there will be no extreme deficiencies or excesses in the mixture. It also makes it likely that leaf protein from different species will be similar. The well-known aminoacid deficiencies in some seed proteins can occur because the protein of seeds is made up of one or a small number of entities. There is no reason to think that organisms ever have a general inability to incorporate an aminoacid in their proteins so that the absence of, for example, lysine from a seed protein does not lead to the expectation that lysine will also be deficient in the protein from the leaf of that species. The aminoacid analyses published so far bear out these expectations and suggest that leaf protein will be a valuable food; as good as the main proteins of the diet, though not as good as the pre-eminent proteins—casein and egg albumin. This expectation also is borne out by experiment. For pigs [5] the protein is as good as, or a little better than, fish meal, and so-far unpublished findings with chickens and rats give similar results.

Two points can now reasonably be taken as established: by one method or another leaf protein can be made on a technological scale, and it is a useful food. Two further points need intensive study. What types of

1. See *Lancet*, Sept. 19, 1959, p. 389.
2. Pirie, N. W. *Mem. Manch. lit. phil. Soc.* 1959, **101**, 1.
3. Pirie, N. W. *Chem. Ind.* 1953, p. 442.
4. Pirie, N. W. *Food Manufacture*, 1957, **32**, 416; *Nutrition, Lond.* 1958, **12**, 3.
5. Barber, R. S., Braude, R., Mitchell, K. G. *Proc. Nutr. Soc.* 1959, **18**, iii.

leaf could be used as the raw material in those countries where the need is most acute; and how would the protein be fitted into the diets eaten in those countries? The first is probably the more important because the world's immediate need is for more sources of locally made protein rather than for protein made for export by industrialised communities. There already appears to be surplus dried skim milk. In each area of need it would therefore be well if the three main types of leaf were surveyed. These are:

Wild leaves.—On a small scale these are satisfactory but, because they usually grow on land that is unsuitable for cultivation, large-scale collection is difficult. Water plants such as papyrus and water hyacinth are an exception; they would not only be easy to collect but the collection would improve the amenities. It is a pity that, with so much effort being put into eradicating these and other pests, so little is put into finding a use for them.

Waste leaves.—In temperate regions pea haulm and sugar-beet tops are satisfactory protein sources. Attention should be given to leaves from such crops as sweet potato, sugar cane, banana, and cassava. Difficulties may well arise with some of them; but they can be discovered, and perhaps overcome, cheaply in the laboratory.

Special crops.—Only about 100 of the third of a million known plants play a significant part in nutrition. Many of the neglected plants grow luxuriantly, but they cannot be used by normal methods of food technology because they do not produce large seeds or tubers and their leaves are unpalatable to stock. At present, and for convenience, we generally make leaf protein from normal farm crops harvested while young, but, when large-scale production starts, plants or varieties new to agriculture will probably be used. Research has already begun on the selection of plants that would be useful in temperate climates; it has hardly begun in the tropics. For this work it is necessary to have only a pound or two of leaf and the normal equipment of a biochemical laboratory; it would therefore be easy to study a wide range of tropical plants in many different places. Until this has been done it would be premature to think of setting up extraction machinery, but it will not be done until some interest is shown in the possibility of making protein in a locality and setting up machinery there.

Specially grown crops, unlike the other two types of raw material, would compete directly with conventional methods of using land. Their advantages are that, even with the crops we have already tried, a greater or more valuable yield can often be got in this way from a given area in a given time, and that a crop, harvested in the vegetative state, is less vulnerable to some pests and diseases than one that has to mature.

PRESENTATION ON THE TABLE

A new type of food can be thought of as something for tiding over a temporary emergency; ideally it should then have little colour or flavour so that it can, according to the usual tradition, be added to bread. If such a product were being made from leaves it would have to be made in an industrialised community and would then be given or sold to the community suffering the emergency. By extraction with fat solvents, leaf protein can be given this form. I have already argued that this is not the present-day position; the need is likely to be permanent, and what is needed is something that can be made in the region where it is to be eaten. This probably means that the leaf protein used in practice will be intensely green. There is no reason why a food should not be green, but it is so unusual as to raise some æsthetic problems.

Most of our experience in presenting leaf protein on the table has involved meeting British prejudice; and this, at first at any rate, is opposed to a dark green soup or stew. We have therefore concentrated on what may be loosely called " cocktail snacks " in which the protein is encased in thin pastry or batter. It has little or no flavour of its own, and what it has is easily masked by the normal flavouring agents. This type of presentation is not altogether unrealistic because a novel protein should not be expected to satisfy more than 10% of the daily protein need; this amount goes into 5 to 10 of these " snacks ". On this scale the protein has been eaten by scores of people, generally with satisfaction and never with more than the routine complaints that one must expect to find levelled against a new foodstuff. Scotsmen are familiar with this reaction on the part of the English towards haggis, and there are reciprocal reactions. If 20 g. or more is eaten at one time, part of the chlorophyll escapes destruction in the gut and appears in the fæces. Again there is, in principle, no objection to a green colour, but anyone intending to eat the protein in bulk should be forewarned so that the green will not be taken as evidence that the protein has not been digested.

So far there have been few trials with the protein incorporated in the foods eaten in the undernourished parts of the world, because people in Britain tend not to be interested in this type of food whether it contains leaf protein or not. This is an aspect of the work on which I would welcome cooperation. Air transport, or some form of refrigerated surface transport, makes it easy to send protein made at Rothamsted in 5–50 kg. lots to many parts of the world, and material made here is probably better than what would at first be made by a new unit working on new types of leaf. We will very willingly send protein to anyone who wishes to undertake a serious study of its acceptability and nutritive value in man, especially in a region that is now undernourished.

This article has dealt with only one deficiency—protein. It is probably the most widespread and important nutritional deficiency in the world today, so that it could be argued that most research should be concentrated on it. But the argument does not depend on that being true. So long as it is agreed that protein deficiency is widespread there is a strong case for searching for new sources of edible protein. Leaves are not the only such source, but they are one potential source which is at present being investigated too little. My aim here has been to describe the present position and point out what can usefully be done immediately without expensive or elaborate organisation.

SHORTAGE OF MIDWIVES

FOR some time past the Central Midwives Board have forecast that the rising birth-rate would soon strain the maternity services. In their report for 1958–59 [1] they are unhappily able to record the truth of their prophecy. During the past year shortages of trained midwives in hospitals approved as training-schools were continually brought to their notice, yet these hospitals are more fortunate than non-training schools in attracting staff. There are also widespread shortages of domiciliary midwives, and the Board reiterate the importance of a fully staffed domiciliary and hospital midwifery service. Their warning is reinforced by last year's figures; for, though on March 31, 1959, there were 67,768 names on the Midwives Roll (an increase of 3046 on the preceding year), during 1958–59 only 16,445 midwives notified their intention to practise—261 fewer than in the previous year.

1. Obtainable from the Board, 39, Harrington Gardens, London, S.W.7. Pp. 16.

COLLEGE OF GENERAL PRACTITIONERS

THE college has completed its seventh year with a formidable account of effort and achievement.[1] Its annual reports have fallen into a pattern in which the sustained enthusiasm of the members is a constant theme. In the past year the college has consolidated its position at home by raising its members' subscriptions, and extended its interests abroad by fresh contacts with its sister colleges in Australia and Canada.

The three main committees of the college, devoted to undergraduate education, postgraduate education, and research, report continued expansion. No medical student need now qualify without an introduction to general practice, and the college has affirmed its belief that all intending specialists would benefit from post-graduate experience in general medical practice.

One new report this year is that of the endowment steering committee, which forecasts a college appeal. In its short life the college has begun an academic trans-formation of general practice, which it can continue only on a basis of sound finance.

ANNUAL MEETING

The seventh annual general meeting, held in London last Saturday, was attended by some 275 members and associates. Dr. G. F. Abercombie was elected president for 1959–60.

Dr. F. M. Rose, chairman of council, said that more than 5500 members and associates had joined the college since its foundation; in the past year 344 candidates were admitted to membership and 345 to associateship. The number of regional faculties was now 34 (United Kingdom and Eire, 25; New Zealand, 4; Kenya, 1; South Africa, 4). The college was proud of its work in both undergraduate and postgraduate education; its medical recording service was proving an outstanding success; its journal, published quarterly, was increasingly valuable; and its Memorandum for the Guidance of Trainers had been very well received. The amount of work done by the college research organisation continued to surprise everyone. With nearly 700 names on the research register, seven college-sponsored projects had been completed and published; sixteen more were under way. Forty-two faculty-sponsored projects had been undertaken, of which the results of eighteen had already been published. A large number of doctors had visited the practice equipment and premises room at college headquarters, and the library was rapidly growing.

Discussion took place on a resolution saying that the time has now come for the college to institute an examination for admission to the membership, and proposing that this should be introduced for those who will register with the General Medical Council after Jan. 1, 1960. This resolution received just less than three-fourths of the votes cast and was therefore lost.

Honorary fellowships.—Dr. I. D. Grant (Glasgow), Dr. L. H. Cordery (New Zealand), Dr. W. V. Johnston (Canada), Dr. H. M. Saxby (Australia), and two members of the steering committee—Dr. J. D. Simpson (Cambridge) and Dr. J. Campbell Young (Belfast)—were appointed honorary fellows of the college.

Butterworth gold medal.—Dr. T. E. T. Weston (London) received the 1958–59 medal for an essay on The Child is Father of the Man. The subject for the 1959–60 essays will be Television and Health. They must be submitted by Sept. 17.

Upjohn travelling fellowships were presented to:

J. A. D. Anderson, J. B. Bamford, S. J. Carne, P. F. Cawley, M. B. Clyne, S. D. Coleman, G. R. Cubitt, Katharina Dalton, Margaret Dudley-Brown, F. B. P. Evans, J. S. Happel, P. D. O'Beirne, D. C. Saunders, M. T. Sweetnam, F. F. Temple, and G. H. Warrick.

Public Welfare Foundation prizes were presented to the following final-year students:

J. G. Adamson, M. L. Dorfman, Bridget Hackett, and D. A. Shedden (Edinburgh), A. Barabas (Manchester), and W. S. Marson (Glasgow).

At the meeting of the new council, held later, Dr. Annis Gillie was appointed chairman, Dr. K. M. Foster deputy chairman, Dr. H. L. Glyn Hughes hon. treasurer, and Dr. J. H. Hunt hon. secretary.

1. Report for 1958-59, issued by the college, 41, Cadogan Gardens, London, S.W.3.

GENERAL MEDICAL COUNCIL

IN a presidential address to the Council at the opening of its 199th session on Nov. 24, Sir DAVID CAMPBELL said that in 1951, when arrangements for the compulsory year of house-officer service were under discussion, it was agreed that the Council should publish a list showing the hospitals and posts approved for this purpose in the United Kingdom and in the Republic of Ireland.

The first list, published in September, 1952, contained 634 hospitals and 3048 posts. The third edition, now in the press, contained 775 hospitals, of which 572 were in England and Wales, 119 in Scotland, 27 in Northern Ireland, and 57 in the Republic of Ireland. There were now 3581 recognised house-officer posts in the British Isles, of which 3274 were in the United Kingdom. Of the latter, 1337 were in medicine, including its specialties, 1548 in surgery, including its specialties, and 357 in midwifery; 32 offered mixed experience.

In May the executive committee recognised degrees granted by the University of Osmania after Aug. 15, 1951, to students of the Osmania Medical College at Hyderabad. This decision brought the number of medical colleges in India recognised by the Council to 27. The previous day the committee had decided to recognise the M.B., CH.B. degrees granted by the University of Natal.

Visiting Ceylon, Sir David had found that one problem was an adequate supply of Western-trained doctors. The authorities had suggested that the number of students at Colombo might be doubled. The faculty of medicine had gone a certain way to meet the demand, but were of the view that to go further would lead to a lowering of standards. An admirable solution would be the establishment of a new medical school at Paradeniya.

At the University of Western Australia an effort had been made to introduce an integration and flexibility which seemed perhaps to be more readily attainable in a new school, such as this, than in an older one. The organisation of the curriculum showed a lively experimental approach of a character which the Council hoped would result from its latest Recommendations. The professoriate were young, enthusiastic, and clearly capable of undertaking the type of team-work which their curriculum demanded. The executive committee had accepted a recommendation that the degrees of M.B., B.S. granted by the university be recognised by the Council.

In Australia there was a great demand for entry into the medical schools; and the Government had established a new university—the University of New South Wales—to which would be attached a medical school. In Victoria proposals were being discussed for the establishment of a second university with a medical school in Melbourne, and in South Australia and Queensland the possibility of establishing new schools was being considered.

In New Zealand the Government had decided that a new medical school was required and should be located in Auckland as part of what would be the university there.

In Canada Sir David had visited the capital cities of the provinces of Alberta, Saskatchewan, and Manitoba, with which the Council had reciprocity. The registrars in these Provinces had asked him to draw the attention of intending medical immigrants to three points:

(1) They should before entering Canada seek the advice and guidance of the registrar of the Province they proposed to enter; (2) if possible they should visit, preferably with their wives, the place in Canada in which they intend to practise; and (3) they should bring with them all the essential documents such as proof of their qualifications and certificates of good standing, which were issued by the G.M.C.

Points of View

FUNDAMENTAL DEFECT IN FIBROCYSTIC DISEASE OF THE PANCREAS

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THE first attempt to find the cause of fibrocystic disease of the pancreas was probably that by Kornblith and Otani (1929), who suggested that stenosis of the pancreatic duct was the cause. Soon, however, it was shown that in fibrocystic disease lesions were not confined to the pancreas and that a simple local mechanised obstruction could not give rise to such a complex condition.

Many other suggestions have been advanced. All fail because they do not explain the known facts. The main pathological features, which must be fitted into any hypothesis, are as follows:

1. Fibrocystic disease is a generalised disease which affects many different types of secreting glands.
2. It is characterised by excessive secretion of mucus, which is clearly seen in the small intestine in meconium ileus but almost certainly occurs also in the bronchi.
3. Brunner's glands differ significantly from the intestinal and bronchial mucus glands in that they produce a totally different type of mucus, which biochemical examination shows to be a mucoprotein instead of an acid mucopolysaccharide.
4. The mucus produced in fibrocystic disease is biochemically normal mucus. No abnormality has been noted on histochemical examination or on enzymatic hydrolysis (Roberts 1957).
5. The abnormality of excessive secretion is not confined to mucus glands as most previous workers have suggested. Secretion of sweat is excessive both in volume and in total solids (di Sant'Agnese et al. 1953). The sweat-glands, however, show no gross histological abnormality.
6. In all early cases of fibrocystic disease zymogen granules are absent from the pancreas, whose canaliculi are distended with plugs of secretion. This is the picture of sustained oversecretion by serous glandular cells.
7. The submaxillary salivary glands also show absence of zymogen granules.

Fibrocystic disease is thus a generalised disease affecting all glands of external secretion. Farber (1944) thought of the disease as a generalised affection of mucus glands only, and consequently suggested the name " mucoviscidosis ". While many workers have thought that the main abnormality consisted in the production of mucus which was abnormal in viscosity and in chemical composition, it seems probable that the mucus produced is normal chemically and the abnormal viscosity of the secretion is due only to an abnormally high proportion of mucopolysaccharide in the mucus gel. The observation that the secretion in Brunner's glands also is excessive leads to the conclusion that the disorder is not an inborn error in the production or metabolism of acid mucopolysaccharides, but one of widespread oversecretion. The serous cells of both the pancreas and salivary glands are abnormal in all cases which I have seen; and, while salivary amylase is greatly diminished in most cases, in a few it is substantially increased above normal.

Evidently, therefore, any suggested cause must take into account three main facts: (1) the general picture is one of over-secretion; (2) the disease affects glands through the body; (3) four distinct types of glands with different secretions are affected.

Apparently, therefore, the primary abnormality in fibrocystic disease is persistent over-stimulation of the secreting glands. The close resemblance between the pancreas in early cases when the serous cells are degranulated and the intra-acinar canaliculi distended with secretion, and the pancreas following experimental injection of pilocarpine is striking. These features all suggest that the cause is some fundamental abnormality or defect in the control of secretions. In the normal subject stimulation of the neural end-organs involves the release of acetylcholine, which causes the glandular cells to secrete. Following this line of thought it seems reasonable to suggest that all the protean manifestations of the disease can be explained either by over-production of acetylcholine or some analogous substance, or else by some failure in its normal destruction whereby it acts for an unduly long time.

The experimental inoculation of such a substance produces an excessive secretion of mucus, discharge of zymogen granules from serous glands, and over-production of sweat (Cushny 1941). The different glands mentioned above, except the sweat-glands, have this in common: they are all supplied and their secretion is controlled, by parasympathetic nerves. Impulses passing along these nerves (sometimes referred to as cholinergic) act by the release of acetylcholine or a closely related substance at their end-organs. Although the sweat-glands are supplied anatomically by sympathetic nerve-fibres, they are anomalous as they are induced to secrete, not by adrenaline, but by acetylcholine and so are usually regarded as cholinergic glands. I personally regard the involvement of the two groups of glands, with such a different anatomical innervation, as good evidence that the disease does not consist in an anatomical abnormality of innervation as in Hirschsprung's disease.

This close correlation between the observed abnormality of secretion and changes on physiological stimulation of the cholinergic glands suggests that the fundamental cause of fibrocystic disease is some abnormality in humoral transmission of nerve-impulses to secretory glands. Normally when a gland is stimulated acetylcholine is liberated at the nerve-endings. Once the acetylcholine has been liberated its action is controlled and is usually only of short duration, as it is rapidly broken down by choline esterase which is present in large amounts in blood and in certain tissues. If the specific choline esterase were diminished in amount, or alternatively the acetylcholine was more resistant than usual to the action of acetylcholine esterase, then the acetylcholine released would act abnormally long and so would cause oversecretion by the glands. Alternatively, the amount of acetylcholine released at the nerve-endings might be excessive. While I am unable to produce strong reasons against this suggestion, I do not favour it and think that the likely abnormality in fibrocystic disease of the pancreas is the physiological opposite of myasthenia gravis, which is due to diminished production of acetylcholine or increased resistance to this substance.

Two separate reported observations support this explanation. First, Farber (1942) claimed to have produced fibrocystic disease in cats by the injection of pilocarpine—an observation which has never been confirmed. Secondly, Ayers et al. (1950) cut the vagus nerve in five cases of fibrocystic disease and found that the duodenal juice contained trypsin four days after the operation. Although this report is unsatisfactory, as the follow-up of the patients was very short, yet it gives useful confirmatory

evidence. It suggests that in fibrocystic disease failure of pancreatic secretion is not due to blockage of the larger ducts by mucus and eosinophilic concretions or to crushing and destruction of the acinar tissue by fibrosis; further, it indicates that the acinar tissue and the duct system are not really so badly damaged as they appear to be on histological examination, as they are capable of rapid regeneration and secretion. An apparent paradox is that section of the vagus nerve should cause the pancreas to start secreting although normally it is stimulation of the vagus which elicits secretion. The explanation may be as follows. The histological appearance of the pancreas and salivary gland are those of exhaustion and suggests that they are being constantly over-stimulated for a long time. While this stimulation persists the granules have no chance to reform, and as a result secretion from the glands contains no enzyme. When the vagus nerve is cut the pancreas is relieved from incessant over-stimulation, the zymogen granules reform, and thus the duodenal juice soon contains normal pancreatic ferments.

It is a pleasure to record the encouragement and assistance I have received from Prof. S. Graham, Dr. A. M. MacDonald, and the staff of the Royal Hospital for Sick Children, Glasgow.

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Medicine and the Law

Non-communication: Appeal Allowed

ON Oct. 18, 1955, a butcher was boning a piece of meat when the knife slipped and caused a wound in his abdomen.

A telephone call for a doctor and ambulance was sent to a cottage hospital with no resident medical staff. A general practitioner, Dr. R., who happened to be there when the message came, arranged for a bed to be held at a nearby general hospital, went to the man's place of work, made a quick examination, and had him sent to the cottage hospital, where he examined the wound carefully. He concluded that though the deep fascia had been cut the wound had not penetrated the peritoneum; accordingly he had the wound stitched and dressed and sent the man home, giving him emphatic instructions to see his own doctor that evening. Dr. R. cancelled the bed at the general hospital. When the man's own doctor arrived, abdominal pain and nausea had developed. The man told his doctor that the hospital had said that the wound was " superficial ", but his own doctor, not appreciating that the hospital was a cottage hospital or the status of Dr. R., examined his patient and diagnosed a digestive order. During the following 36 hours the man's condition deteriorated, and on Oct. 23 he died in hospital after operation. A postmortem examination disclosed a penetration of the small intestine.

The man's widow brought an action alleging negligence against Dr. R. on a number of grounds, including the allegation that he had been negligent in failing to communicate directly with the man's own doctor by letter or telephone to inform him of exactly what had happened and of his own findings. The doctor denied negligence. The trial judge [1] dismissed all the charges of negligence save that based on failure to communicate with the man's own doctor. On that he found Dr. R. negligent and awarded the widow agreed damages of £9050. The doctor appealed. The Court of Appeal, by a majority, allowed the appeal.

Lord Justice MORRIS, in the dissenting judgment, said that Dr. R.'s diagnosis that the wound was superficial was clearly wrong; but it was not negligent.

It was now clear that it would have been desirable to have kept the patient under skilled observation, for if that had been done the man's life would have been saved. Everyone was agreed that there was need to call in the man's own doctor. Why was that? It must have been because the nature of the wound was such that the possibility of a wrong diagnosis could not be ruled out. Yet the melancholy fact emerged and remained that the patient's own doctor was never made aware of that but was led to think that he need not concern himself with the wound. That doctor was in no way criticised. But if he had received a communication from Dr. R. he would have been made aware of facts which were not within his knowledge. The patient was stitched up and bandaged; there was no wound to be seen; and the patient had been authorised to tell his doctor that the hospital had decided that the wound was superficial. If it was justifiable for the patient to return home provided he was under skilled supervision, the imperative necessity arose to make sure that the doctor was made aware of the reason why he was being called in. Yet the man's own doctor, not being negligent, never appreciated the real reason for that.

The question whether the omission to communicate with the patient's own doctor was negligent must be a matter for the Court, and if medical witnesses stated that if they had been similarly placed their conduct would have been no different, the duty of the Court to decide whether such conduct amounted in law to negligence still remained. There had been such medical evidence in this case, but it had not persuaded his Lordship that the Judge's finding of negligence on this limited issue was faulty. He would dismiss the appeal.

Lord Justice ROMER, allowing the appeal, said that Dr. R.'s examination was conducted with skill and care and led him to conclude that there was no more than an outside chance that the peritoneum had been penetrated. All that he subsequently did on Oct. 18, 1955, was consistent with and founded on that wrong diagnosis. But the case depended on whether he was professionally negligent. Two medical gentlemen of eminence and experience had given evidence to the effect that nothing Dr. R. did or did not do was open to any criticism. His Lordship was not prepared to hold that any action or conduct which those two gentlemen regarded as reasonable constituted professional negligence. He was aware of no case in which a medical man had been held guilty of negligence when eminent members of his own profession had expressed on oath their approval of what he had done. His Lordship was satisfied that in no way whatever should Dr. R. be regarded as guilty of professional negligence, as distinct from having made a pardonably erroneous diagnosis.

Lord Justice WILLMER, also allowing the appeal, said that if the finding of negligence against this doctor stood, its results would go far beyond this case and might well affect the whole of his future professional career, particularly where a man had died.

The plaintiff's case was based on the fact that the patient was told to tell his own doctor that the wound was superficial. That was a misapprehension of the evidence. Nobody suggested that the patient's own doctor was negligent; but it was vitally necessary to consider what he knew or had the means of knowing, and what Dr. R. ought to have contemplated the man's own doctor would know and have the means of knowing, before deciding that it was

1. See *Lancet*, 1958, ii, 1118.

negligent not to communicate directly and inform him that the deep fascia had been found to be cut.

The man's own doctor knew that he had stabbed himself with a butcher's knife; he knew the location of the wound, and as a medical man must be taken to have known the dangers of such a wound. He knew that Dr. R. thought it was only superficial; but he must also have known that the wound was at least deep enough to call for a probe and a stitch and that the patient had been insistently told by Dr. R. to call him in that evening. Moreover, he knew, as Dr. R. did not know, of the complaint of abdominal pain and nausea. If, therefore, Dr. R. was to be held negligent, why was the patient's own doctor not in like case?

The fact was that the action of the patient's own doctor was conditioned by an unfortunate misapprehension as to the nature and status of the cottage hospital and Dr. R. No-one was to blame for that and it was something which Dr. R. could hardly be expected to foresee; nor would the mere sending of a letter or other communication have removed that unfortunate misapprehension. In all the circumstances and in the light of the evidence the finding of negligence could not be supported.

CHAPMAN *v.* RIX.—*Court of Appeal* (Morris, Romer, and Willmer *L.JJ.*); Nov. 18, 1959. Counsel and solicitors: G. G. Baker, Q.C., and Peter Webster (Hempsons); N. R. Fox-Andrews, Q.C., Roger Ormrod, Q.C., K. M. Willcock and Christopher Besley (Leonard Tubbs & Co.)

M. M. HILL
Barrister-at-Law.

Public Health

Dangerous Cranberries?

IN late November every year the people of the United States celebrate Thanksgiving, to commemorate the thanksgiving of the Pilgrim Fathers for the abundance of that first harvest which enabled them, or some of them, to survive their first American winter. The annual celebration, which ranks with Christmas and the Fourth of July, entails the consumption of millions of turkeys, which in turn entails the consumption of millions of dollars' worth of cranberry sauce.

Aminotriazole is a weed-killer that the Department of Agriculture has approved for use on cranberry crops provided it is applied only after a crop has been harvested; but the Food and Drug Administration has refused to endorse its use at all because tests by one of the producers of aminotriazole have shown that it may induce thyroid tumours in rats. There was, therefore, great consternation among the cranberry growers (and eaters) of the nation when on Nov. 9 Mr. Arthur Flemming, Secretary of Health, Education, and Welfare, announced that parts of the crop from Washington and Oregon had been found by the Food and Drug Administration (part of his department) to be contaminated by aminotriazole applied before the crop was harvested; and he advised housewives not to buy any cranberries if they did not know where they were grown—though the States concerned produce only 8% of the total crop, which is expected to be a record one this year.[1] Feverish nationwide testing of crops has begun—so far almost all the samples tested have been declared free of contamination [2]—and the cranberry growers have called on the President to declare their regions disaster areas, in view of the economic catastrophe they face.[3]

Meanwhile many of the prospective candidates for the Presidential campaign next year have been vigorously eating cranberries; various eminent doctors have belittled the possible ill effects of aminotriazole; and Dr. Boyd Shaffer, who discovered the tumour-producing effect of the drug, has said that a person would have to eat 15,000 lb. of contaminated cranberries daily for many years to suffer any ill effect. Perhaps the celebrations will not be too severely dampened.

1. *New York Times*, Nov. 15, 1959.
2. *Christian Science Monitor*, Nov. 17, 1959.
3. *Boston Daily Globe*, Nov. 16, 1959.

Conferences

OCCLUSIVE ARTERIAL DISEASE

FROM A CORRESPONDENT

A CONFERENCE at the Royal College of Physicians of London on Nov. 13 and 14 was concerned with the pathogenesis and treatment of occlusive arterial disease.

Pathogenesis

Reviewing the histological features of the atheromatous plaque and the theories propounded to explain it, Prof. J. H. DIBLE supported Duguid in his contention that the lesion was initially a thrombus which became epithelialised and later degenerated. Prof. C. V. HARRISON referred to other occlusive arterial diseases, discussing pulseless disease, giant-celled arteritis, Buerger's disease, polyarteritis nodosa, scleroderma, and thrombotic microangiopathy.

Sir HOWARD FLOREY gave a clear and concise review of experimental atheroma, regretfully acknowledging that so far it had not proved possible to produce any lesion experimentally that was unanimously accepted as being the same in all respects as the human atheromatous plaque. He also drew attention to the continuous passage of lipids through the vessel wall; any local trauma could interrupt this passage and cause a local accumulation of fat in the vessel wall.

Dr. G. J. POPJAK gave an expertly simple account of cholesterol metabolism, emphasising the importance of endogenous production of cholesterol. The possibility of suppressing endogenous cholesterol metabolism in man by means of continuously administered synthetic substances, farnesyl and farnesoic acid, stems directly from Dr. Popjak's researches.

Dr. C. F. POOLE discussed his experiments on the formation of artificial thrombi in vitro. He had fashioned a circular plastic tube, paying special attention to the joint, so that a uniformly smooth surface was offered to the contained blood. By continuously rotating the tube about a horizontal axis, the flow of blood was simulated. In these circumstances he found that within a minute clumps of platelets, polymorphs, and monocytes formed and coalesced; these were the normal constituents of the "white head" of a thrombus. In about five minutes this conglomeration was joined by fibrin and red cells, the structures which made up the "red tail" of a natural thrombus. Either heparin or prothrombin deficiency interfered with the normal clotting of blood; neither prevented the formation of the "white head" of the clot, but both stopped the appearance of the "red tail".

Prof. G. PAYLING WRIGHT spoke about the development of a thrombus in vivo, showing beautiful electron micrographs of platelets, and about the changes in their structure which followed their adhesion to a water wettable surface. He emphasised the key role of the platelet in initiating the formation of a thrombus in vivo.

Cerebral Vascular Disease

Describing the basilar-carotid artery syndromes, Dr. E. C. HUTCHINSON pointed particularly to the possibility of focal changes in the brain far from the site of the underlying arterial disorder. This must have wide implications in clinical neurology. Dr. J. W. D. BULL discussed the radiological investigation of acute strokes, and showed some striking radiographs. The angiogram and encephalogram might be normal despite the presence of an intracerebral hæmatoma.

Mr. WYLIE MCKISSOCK discussed the surgical treatment of acute strokes, and Prof. C. G. ROB the surgery of the carotid and vertebral arteries. Dr. D. A. SHAW and Dr. J. MARSHALL, discussing medical treatment of acute strokes, both advised against the indiscriminate use of anticoagulants. Replying to questions about the selection of cases for surgical treatment, Mr. MCKISSOCK said that in his view age up to 70 was itself no barrier; the level of consciousness was the best guide to prognosis after surgical treatment. Those patients who were alert or only drowsy did best, whereas most stuporose or comatose

patients died. In all, he claimed a 25% total survival after ten years. Professor Rob was asked where exactly he listened in the neck to hear the murmurs over the carotid or vertebral arteries, and there followed the instructive example of a surgeon explaining the principles of auscultation to an attentive group of physicians. Further discussion centred on whether anti-coagulants had any place at all in the treatment of cerebral vascular disease, and the difficulties of differentiating hæmorrhage from thrombosis were mentioned. Dr. MARSHALL's view was that there was a place for anticoagulants in the treatment of brain-stem lesions in normotensive subjects.

Coronary-artery Disease

Prof. J. N. MORRIS, discussing epidemiology and diet in relation to coronary-artery disease, said that whereas coronary atheroma had actually decreased in the past fifty years, coronary occlusion had increased. He emphasised the value of exercise in preventing coronary disease, and showed how coincident hypertension worsened the prognosis, especially in older patients. In younger patients high blood-lipid levels seemed of more importance, but he could find little support for a relationship between dietary fat and coronary-artery disease. There was a need for field surveys, and age, sex, smoking, and activity were probably the most important ætiological factors. If Professor Morris's views are correct, and they passed uncontradicted in this distinguished audience, there has been a staggering waste of time and money in following false trails both here and, more particularly, in the U.S.A.

Dr. M. F. OLIVER spoke on the remarkable difference in the incidence of coronary-artery disease between men and women, and doubly and trebly proved his points by reference to women after the menopause, those who had had premature menopause, and men who had been castrated. He also showed that the incidence of coronary-artery disease in women who had had four or more pregnancies was significantly higher than in those with three or less.

Dr. A. G. LEATHAM described coronary angiography, a promising experimental technique for the display of the coronary tree, so far only applied to dogs; and Prof. T. CRAWFORD showed some instructive radiographs of the coronary vessels obtained by postmortem injection. Prof. R. S. PILCHER described his experiments in the surgical treatment of coronary-artery disease in dogs.

Dr. A. R. GILCHRIST spoke forcefully and convincingly on the value of anticoagulant therapy in coronary disease; and Dr. ROSEMARY BIGGS discussed the laboratory control of such therapy, its difficulties, limitations, and cost, and the major problems that would be created by the widespread use of long-term anticoagulant therapy.

Prof. J. MCMICHAEL agreed that this form of treatment should be used in acute coronary thrombosis, but was less convinced of its value as a long-term procedure. He examined the recent M.R.C. report in some detail, and found it wanting in many respects. Sir GEORGE PICKERING replied to these criticisms, and Dr. M. TOOHEY clarified some points about his work which had been referred to.

Peripheral Vascular Disease

Dr. E. L. MCDONALD discussed the investigation of peripheral vascular disease, laying particular emphasis on the value of arteriography to localise the site of obstruction. Dr. H. BANCROFT spoke of the role of the sympathetic nervous system in the control of blood-vessels, and the limitations of sympathectomy in the treatment of human disease. Dr. W. G. OAKLEY detailed the clinical patterns of peripheral vascular disease in diabetics, and his experience in their treatment. Dr. J. F. GOODWIN outlined the medical treatment of peripheral vascular disease, stressing that alcohol was the only really good vasodilator, and that in very high dosage, and that tobacco should be avoided; and Mr. G. W. TAYLOR gave an account of the surgical treatment.

The proceedings of this stimulating and informative conference will be published later as a book.

In England Now

A Running Commentary by Peripatetic Correspondents

WHEN I go somewhere, I like to have an object; and the object of my visit to the United States was to see a chipmunk. Though 59 years of age, I had never actually seen a chipmunk; and, to the best of my belief, no chipmunk had seen me. Time, I felt, was running on.

No difficulty at all, said the man on the boat. In Maryland last summer there'd been hundreds of them, eating out of his hand. And weren't they cute! But, alas, the Foundation from which my British-American Chipmunk Discovery Expedition was drawing generous but unwitting support didn't send me to Maryland. In Central Park, New York, I drew blank: someone, it seems, has written a book saying that on Manhattan Island you can still see pretty well any known animal or bird; but all I saw was a horse. A drive through New Jersey promised better; but, if I have any criticism of the wonderful new American road system of parkways and driveways and turnpikes, it is that they are ill suited to recognising chipmunks. I calculate that if one is travelling at 65 m.p.h., and the chipmunk, moving tangentially at 8 m.p.h., is 20 ft. from the curb (and probably inside a bush), the time during which one's eye will rest on it is—well anyway quite short. And American drivers on turnpikes seem curiously reluctant to stop and examine passing plants or animals.

The day we drove up-State, in clear chipmunk weather, my host was very hopeful; and we ended up in splendid chipmunk country settled by Dutch patroons in the middle of the 17th century. I can only hope my face did not fall too obviously when, instead of getting a happy hour round the woodshed, I found myself in the middle of a large party of doctors and psychologists and their wives. Ces sont magnifiques, I said (as indeed they were), mais ils ne sont pas les chipmunques.

And so it went on. In Boston I eagerly accepted invitations to the suburbs; and I met a radiologist who said that last winter the drapes or curtains of his country cottage were eaten by chipmunks—though he bore no malice. Rather irrelevantly, I thought, someone else told me that his dog had chased a ground-hog (which turns out to be a kind of marmot); and I was assured that in Wisconsin I should see gophers. I need hardly tell you that in Wisconsin, though driven for hundreds of miles, I did not see a gopher or anything else, unless you count some white rabbits in the university farm at Madison; and I was rather hurried past these. My Madison host, a pædiatrician, said that the chipmunks in his garden were ridiculously tame but his boys chased them. Which brings up the question whether nowadays we are getting quite the right type of pædiatrician.

Passing through Pennsylvania and West Virginia, also mostly at 65 m.p.h., I bring you at last to a small but now historic town in North Carolina. Can you blame me if I say that by this time my heart-rate rose but little when my new host made the customary statement about the prevalence of chipmunks in his woodpile? The morning would show. And indeed, when morning came, there were only regrets: the day was so dull that neither beast nor bird was astir; and anyway the woodpile had been badly disturbed—suitably enough—by the coloured garden-boy. At this, anyone whose second name wasn't Spider would have given up; but I went back for one last look. Wonder of wonders and hurrah!—at this very moment, when all seemed lost, the only remaining chipmunk in Eastern America skipped out of a flowerbed, flicked me a glance, and skipped back again. Yes, Sir, it looked cute; and I only hope I looked cute too.

P.S.—In Wisconsin, I hear, visitors to the medical school are known as Visiting Chipmunks! I wonder why?

* * *

There was what I suppose might be described an important ceremony in the Senate House last week, when we were all accepted as members of the University. The standard of marching from the college to S.H. was appalling, even with Colonel Bogie to help us. I had never before seen a hundred

people in a body, and no two in step. I think it may have been a conscious revolt against what some considered excessive militarisation of the academic ceremony of Matriculation. Once in the ceremonial hall, we shuffled a pace forward, lowered our eyelids in the direction of a bored-looking deputy deputy deputy vice-Chancellor, and shuffled off right. That was that —except for immediate resort to coffee to restore our quivering nerves.

* * *

A variation on the triangle theme not propounded by Einthoven appeared in the medical ward lately. A company director recovering from a coronary thrombosis was sitting up in bed fairly comfortably, when into the bed on his left was admitted a tough character with bronchitis—a burglar by profession and of some skill and experience. On his immediate left was later admitted a young police constable with a minor ailment. They had all met before. Patient no. 2 had removed a car belonging to patient no. 1, and patient no. 3 had removed patient no. 2 and the car from the Queen's Highway shortly afterwards.

They were strange bed-fellows, almost more odd than the *Three Men in a Boat*, but just as harmonious, and became *Good Companions*. Both patients 1 and 2 had served with distinction in the trenches in the 1914–18 war, and old comradeship drew them together. " You know," mused patient no. 1 to me, after the others had left, " he was a very good chap, the sort you would like beside you in a tight corner."

* * *

Chang was small and quiet and peaceloving. But the Captain of Boxing glowed. Each year he had looked hopefully at the new intake to the medical school, and here at last was the answer to his dreams. " He must be a flyweight. He can't weigh more than eight stone."

No, Chang didn't have to box; in fact he refused to box and only accepted the invitation to join the boxing team on that understanding. Every year he went to weigh in and represented his hospital through to the final, getting a walkover in each bout. No other team could find a boxer weighing less than eight stone.

His landlady fed him well, and one year he discovered to his chagrin on the day before the weigh-in that he was eight stone five. Being Chinese he was resourceful and a large dose of mag. sulph. took off the necessary weight at the cost of a bad night and not a happy day. He tottered to the scales almost too weak to stand. " Seven stone thirteen." So again he won maximum points. Fluid can easily be replaced if you go to the right place and the Captain of Boxing was prepared to pay.

Chang is qualified now and we didn't win the cup last year. It's a good thing to have a sprinkling of overseas students in our medical schools.

* * *

Notices to candidates for final examination in medicine:

London—" Candidates must write on only one side of the paper."
Edinburgh—" Candidates must write on both sides of the paper."

* * *

AIMEZ-VOUS ROCK 'N' ROLL ?

Mon cher
Ne sois pas *square*
C'est trop naïve
De ne pas savoir *jive*
Car ça fait pousser les cheveux sur la poitrine
See what I mean ?
C'est drôle
Ce joli *Rock 'n Roll.*

À Dieu ne plaise
That I should change your ways
Mais, quoi, pour être *snob*
It is a full-time job;
Vas-y
Courage, petit—
Ou même alors
Tu seras *bore.*

Letters to the Editor

" 140 NEW HOSPITALS OF 800 BEDS "

SIR,—The last annual report [1] of the Ministry of Health reviews the first ten years of the National Health Service and makes interesting reading. In 1949 there were 448,000 hospital beds and 2,937,000 deaths and discharges from hospital. In 1958 there were 477,000 beds and no fewer than 3,889,000 deaths and discharges, almost another million people. The small increase in beds is due to making use of hitherto unstaffed beds. After allowing for these extra beds the increased turnover in hospitals in England and Wales is equivalent to the building of *140 new hospitals of 800 beds*. This increase in work has been achieved mainly by making more effective use of available beds. This has been made possible by medical advances, such as antibiotics and cortisone, by increasing specialisation within hospitals, by reduction in the size of ward units, and by increased medical staffing. It has been accomplished with only a slight increase in cost when 1958 figures are given in terms of the 1950 value of money. Indeed, the London teaching hospitals are now costing less than previously (see p. 79 of the Ministry report). Full credit is surely due to the hospitals for this admirable record of service to the public.

With virtually no increase in cost the hospitals have become 30% more efficient in ten years. However, the limit has now been reached for increase in efficiency without improvement in buildings. The hospital architectural world is bubbling over with new ideas and indeed Great Britain leads the world in this field in spite of the fact that hardly any new hospitals have been completed since the war and old hospitals have received only first-aid repairs, occasional small extensions, and replacement of wornout boilers.

Hospitals have patiently waited while homes, factories, and schools have rightly had the first claim on national capital moneys, but the time has now come when hospitals have surely justified their claim to more rebuilding. Admittedly £30,000,000 is being allocated next year, but it will need at least £50,000,000 a year to make an appreciable impact on British hospitals if even half of them are to be brought up to date within the next ten years. Unfortunately it is inadequately appreciated how many of our hospitals, even those with international reputations, are deplorably oldfashioned and have a dangerously low standard of hygiene in kitchens, wards, and even in operating-theatres. The nurses particularly are still having to work and live under conditions which were out of date many years ago.

All these things can be tolerated if it is known that the problem is recognised by the Treasury, but few have felt that this is so.

In spite of our present inadequacies, the distribution of consultants, the availability of special investigations, and the excellence of nursing care are probably better in this country than anywhere else in the world.

Central Middlesex Hospital,
London, N.W.10. F. AVERY JONES.

RESEARCH AND CLINICAL MEDICINE

SIR,—Professor Donald (Nov. 14) would like to see better facilities and more research done in teaching hospitals. To achieve this he recommends that house-officers should be " at least doubled in numbers ", and

1. Report of the Ministry of Health for the year ended Dec. 31, 1958 Part 1. Cmnd. 806. H.M. Stationery Office.

more junior and middle-grade appointments should be made " to provide the proper opportunities for younger medical men in the non-university areas ". This despite his earlier statement that the existing organisation of academic medicine " causes a large accumulation of men who cannot advance up the academic ladder " and " many proved and talented men cannot find more senior appointments ".

In considering postgraduate medical education surely Professor Donald should look further afield than the confines of the teaching hospital. One of the most important achievements of the National Health Service has been the upgrading and development of the great non-teaching Metropolitan and provincial hospitals. It is now seldom necessary for a patient to be referred from a hospital group such as my own to a teaching hospital, even for the most specialised diagnosis and treatment.

Peripheral hospitals serve the great majority of the population, and if, as Professor Donald believes, in a teaching hospital research and scientific activity mean improved patient care, this is equally true in a non-teaching hospital. Many of these hospitals can now offer the clinical experience and responsibility which Professor Donald hints is often unavailable to registrars in the teaching hospital. Some can also offer research facilities and I am sure that Professor Donald does not believe that clinical research is only possible within the strict confines of the university. Meetings of almost any of the scientific medical societies provide evidence that this is very far from the case. The greater wealth of clinical and pathological material available for study and research projects is in the non-teaching hospitals. Under the inspiring leadership of the late Dr. E. S. Duthie this department, for example, has in the past six years published 18 papers in leading medical and scientific journals, whilst registrars working in it have obtained the M.D., PH.D., and two regional board research prizes.

The big non-teaching hospital groups are having great difficulty in finding housemen and registrars of ability. Their work cannot be carried on without talented young people any more than can that of the teaching hospitals. They serve the great majority of the population, and their patients are entitled to standards of investigation and care as high as those of the teaching hospitals. This the Health Service has recognised. If Professor Donald's advice to double the housemen and increase the registrars in the teaching schools were put into effect a very serious situation would threaten the already hard-pressed peripheral hospitals.

As one who has worked in both kinds of hospital and whose senior registrar has for five years held a joint appointment with the department of pathology at St. George's Hospital Medical School, I am sure that there must be closer association between teaching and non-teaching hospitals. It is very encouraging to read today that Lord Cohen of Birkenhead, speaking in the House of Lords, regretted that there is not enough contact between the regional and teaching hospitals. Joint appointments in the registrar grades can do a great deal to break down the old antagonisms. We in Southampton have certainly benefited much from our association with St. George's.

Royal South Hants Hospital
Pathological Laboratory,
Southampton.

R. A. GOODBODY.

ADAPTATION IN CALCIUM ABSORPTION

SIR,—I should like to make the following obervations with regard to your annotation of Nov. 7 with which I am in substantial agreement.

An attempt has, in fact, been made to define the normal limits of urine calcium on a normal balanced diet [1] and the value of this survey has been acknowledged elsewhere.[2] Briefly, the upper limit of urine calcium for normal adult men is 300 mg. per day and for women 250 mg. per day.

If the concept of a compensatory increase in calcium absorption [3] is accepted, then the treatment of sarcoidosis and idiopathic hypercalciuria by restriction of calcium intake or oral administration of phytate [4] would seem to be inadvisable, since it would be expected to lead to bone demineralisation.

An increased absorption of calcium as evidenced by a low fæcal calcium is also observed in primary hyperparathyroidism,[5] although it is not yet clear whether this is due to a compensatory increase in the intestinal absorption of calcium, as suggested by Jackson and Dancaster,[3] or is the result of a direct stimulatory action of parathyroid hormone on the intestinal absorption of calcium.[6 7]

For some time I have considered that the intestine may adapt to decreased as well as increased renal excretion of calcium. Thus, the increased fæcal excretion of calcium seen in chronic renal failure [8] may be due, at least in part, to a compensatory decrease in the intestinal absorption of calcium in response to the decreased renal excretion. Such a concept would help to explain the resistance to vitamin-D therapy which is often observed in renal failure.[8 9]

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The General Infirmary, Leeds.

A. HODGKINSON.

EXTRADURAL HÆMORRHAGE

SIR,—In your annotation of Oct. 17, referring particularly to the paper by Hooper,[10] a quotation is given to the effect that arteriography " is rarely indicated in cases of extradural hæmorrhage because it takes so long ". We have been long convinced that arteriography has a most important part to play in the management of head injury —so important a part indeed that in our opinion arteriography must be made expeditiously available. When the march of events is rapid, it is of course obvious that delay for special investigation is unjustifiable: and if the clinical picture is unquestionable, arteriography is unnecessary, but this is true only of the minority of cases.

In 1957 in this unit 18 cases of extradural hæmorrhage were operated upon. 6 had immediate operation, and in the remainder arteriography was carried out. In a third of this latter group the clot was demonstrated to lie at a site which would not have been deduced from the clinical evidence. This is our general experience in extradural hæmorrhage.

We find that in some years acute subdural hæmatoma is more common than extradural hæmatoma. Most of these cases have no classical " lucid interval " because of cerebral contusion and laceration. Arteriography is essential to determine whether a massive intracranial hæmorrhage, or swelling of the brain, be present, and to plan the operation with accuracy.

1. Hodgkinson, A., Pyrah, L. N. *Brit. J. Surg.* 1958, **46**, 10.
2. *Brit. med. J.* 1959, i, 495.
3. Jackson, W. P. U., Dancaster, C. *J. clin. Endocrin.* 1959, **19**, 658.
4. Henneman, P. H., Dempsey, E. F., Carroll, E. L., Albright, F. *J. clin. Invest.* 1956, **35**, 1229.
5. Bauer, W., Albright, F., Aub, J. C. *ibid.* 1930, **8**, 229.
6. Talmage, R. V., Elliott, J. R. *Fed. Proc.* 1958, **17**, 160.
7. Firschein, H. E., Neuman, W. F., Martin, G. R., Mulryan, B. J. *Rec. Progr. Hormone Res.* 1959, **15**, 427.
8. Liu, S. H., Chu, H. I. *Medicine, Baltimore*, 1943, **22**, 103.
9. Stanbury, S. W. *Brit. med. Bull.* 1957, **13**, 57.
10. *Brit. J. Surg.* 1959, **47**, 71.

The making of diagnostic burr-holes takes time, which can be a serious consideration if the first burr-holes are negative. Further, subfrontal or infratemporal clots by this method would escape detection, and they are not rare. We have known arteriograms to reveal an extradural hæmorrhage on one side and an acute subdural clot on the other.

The radiologists in this hospital have provided a 24-hour service, with a radiographer in residence at night. This grade of service should be emulated. Prompt arteriography is unquestionably a necessary part of a head-injury service.

D. O. HANCOCK
G. L. ALEXANDER
D. G. PHILLIPS
A. HULME
Frenchay Hospital, Bristol. J. L. G. THOMSON.

LEUKÆMIA AND GEOGRAPHY

SIR,—I am grateful to all those correspondents who have commented on my paper. The additional figures provided by some of them are particularly interesting, and though Dr. Lenihan (Nov. 14) and Dr. Hargreaves (Nov. 7) disagree with my hypothesis I think the figures they provide can be used to support it.

Dr. Hargreaves gives figures for the years before 1950 and shows that over the longer span Westmorland and Brecon do not show any startling increase in leukæmia death-rates. However, if one uses the period 1947–53 as the new reference level Westmorland shows an increase of 25%—still high enough to be interesting. Brecon shows no increase but its elimination only helps to tidy matters up because there are figures available which indicate that fallout in parts of that county are not very high.

Dr. Lenihan provides figures for Scotland. The effect of them is to give us another four counties whose leukæmia death-rate has risen by over 50%. The eight counties now known to have suffered thus are: Ayrshire, Inverness-shire, Ross and Cromarty, Wigtownshire, Cumberland, Montgomery, and Monmouthshire.

I do not know of any statistical check that can be applied to the figures which entitles anyone to say definitely that these increases are such as would be caused by chance. What seems to me to make such an explanation unlikely is the fact that the increase has occurred in counties of a certain topography and has not occurred elsewhere (except perhaps in Cambridgeshire). That there are some mountainous counties where no increase is yet apparent does not upset the argument because under-diagnosis of leukæmia is quite likely to occur in remote rural areas. Its over-diagnosis, anywhere, is virtually impossible.

Dr. Hammet's letter of Nov. 14 is to be welcomed as a reminder of the time factor. The average "incubation period" for radiation-induced leukæmia is six years though the disease can occur sooner. Six years after 1945 brings us to 1951, and allowing an interval for the incorporation of ^{90}Sr in bone and the subsequent death of the patient one would expect the rise in death-rate to be reflected for the years from 1952 onward. From this point of view I am sorry to have had to choose a year as late as 1954 to commence my second period. However, 1954 may turn out to be a key year after all because it was the year of Bikini and the greatly increased atmospheric pollution caused by the hydrogen bombs. I shall look forward with interest to the leukæmia figures from 1960 onwards. Will the extra ^{90}Sr we have consumed since 1954 cause a further rise in the death-rate? By 1965 we shall probably know for certain one way or the other.

It remains for me to deal with Dr. Loutit's vigorous letter of Nov. 21. The figures to which he refers were mostly known to me and some of them were quoted in the article. He says that the annual dose to bone would be some 2·5 mrad per year per strontium unit, and the figure I gave was 30 mrem for 10 units, so there is no disagreement between us on that point.

Again on the question of the actual levels of radiostrontium in bone, the figures I used were also those of Bryant et al., but I placed emphasis on the highest levels of which I had knowledge. This seems wholly justifiable in view of the small number of samples analysed out of a population, at risk, of 50 million.

Dr. Loutit is convinced that the increasing incidence of leukæmia is not due to radiostrontium. I hope he is right, because radiostrontium is going to be with us for a long time; but I cannot, at present, share his conviction wholeheartedly. If he had been able to suggest an alternative explanation for the different experience of the rainy counties I would have listened carefully because we have certainly not reached the stage at which it is safe to dogmatise.

I avoided dogma and thus by a hair's breadth avoided Dr. Loutit's ridicule (or do I deceive myself?). Yet even had I been so ill-advised as to have drawn firm conclusions from the incomplete data available to me, would I have been behaving less scientifically than Dr. Loutit in his enthusiastic exculpation of ^{90}Sr of all responsibility for the rising leukæmia death-rate?

Caernarvon. T. ALUN PHILLIPS.

SIR,—It is regrettable that Dr. Loutit should imagine that increasing wages are as likely to cause leukæmia as radioactive fallout: in Hiroshima and Nagasaki it was strontium 90, not dollars, with which the inhabitants were showered. Yet there the incidence of leukæmia had within two to three years risen to five times the pre-1945 figures, with a tenfold peak in 1953. It was possible to elicit a history of exposure to neutron and gamma-ray bombardment from the flash, and/or dilute fallout subsequently in from three-quarters to four-fifths of reported cases. It would thus appear that the only doubt still possible is not that a general rise in radiation exposure causes a corresponding rise in leukæmia among survivors, but whether it is conceivable that an increment in radiation when applied generally to a population can be small enough not to be reflected in an equally small rise in the incidence of this disease.

Uniform distribution in bone-salt is not necessarily the "most pessimistic assumption". It is quite conceivable that local deposits in bone, of relatively high concentration, may be expected to increase the probability of significant damage to myelocyte chromatin. There is little evidence that the predominantly high rate of beta emission from ^{90}Sr is not more likely to penetrate through from bone to marrow, than the mainly alpha emission from natural radium and thorium, which, though more intensely ionising, has considerably less range. In bone, the ratio of 10 to 1 for penetration by beta and alpha respectively, measurable in millimetres, may be not insignificant. Even on Dr. Loutit's figures, children about 1 year old are getting not much less than 1/40th of this unnecessary and more penetrating radiation, over and above unavoidable natural dosage. ($2{\cdot}5$ mrad $\times 1{\cdot}5$ S.U. $\times 40 = 150$ mrad per annum.)

That ^{90}Sr should irradiate bone-marrow much more than lymph tissue is hardly argument for exonerating fallout. In Hiroshima the bulk of leukæmia cases were myeloid: lymphatic types were very rare.

Dr. Loutit's statement that (for the thesis that radiostrontium is a possible cause of increase in leukæmia incidence to be correct) the ^{90}Sr rad would have to be of orders of magnitude greater than that of the other components of natural radiation, seems to me to be rather incautious. Why greater,

or even equal to? What proof is there that beta-emitting ^{90}Sr is not more dangerous than, say, radium? Particularly in low concentrations? Is it not true that the areas of our ignorance of the precise mechanism of cell-mutation are such that not only would it be not pertinent but also dangerous to be too categorical? The more so, since otherwise one might well find one's self in the position of having unwittingly sanctioned the possible extinction of human life.

In fact, the confession of ignorance of the ætiology of leukæmia and its non-linear increase, followed as it is by the dogmatic asseveration about what does *not* cause it makes one wonder whether Dr. Loutit has really considered all the evidence. The greatest mystery about leukæmia to me is the reluctance to consider the obvious.

Bilston, Staffs. PAUL HAMMET.

HYPOPHYSECTOMY

SIR,—In your leading article of Nov. 14 you state that in our recent report [1] we "claim that the implantation of two activated sintered rods of ^{90}Y, 6 × 2 mm., with a total dose of 11 mC regularly produces 'virtually complete' destruction" (of the pituitary gland). This statement does not include an essential qualification made by us—that "one source (should be placed) in the centre of each half of the gland". Meeting this qualification, by means of a new technique, is in our view the most significant advance contained in our recent publication.

In our report we emphasised that *free* rods of ^{90}Y cannot consistently be placed in the optimum position and will *not* regularly destroy the gland. In our opinion, and that of Fraser et al.,[2] misplaced rods in the upper part of the fossa may necrose the diaphragma sellæ allowing leakage of cerebrospinal fluid. The incidence of rhinorrhœa in published reports of transnasal insertion of *free* rods of ^{90}Y has been estimated at approximately 20%.[3]

We showed that accurate placing of ^{90}Y rods can be achieved by the method of screw implantation and is consistently followed by 98–100% destruction of the intracapsular portion of the gland. Although this technique was described in detail in 1958 in your columns [4] and further reported in our later paper,[1] it receives no mention in your leading article.

Accurate placing of the ^{90}Y rods by the screw technique has led to a significant reduction in the incidence of rhinorrhœa, and in our paper we reported that this complication developed in 3 of 33 patients who had implants of approximate activity 14 mC. The incidence has been further reduced by lowering the dose to 9 mC (1 out of 43 patients). Postmortem studies have now confirmed that the smaller dose is sufficient to destroy the intracapsular portion of the gland.

Although you state that no danger of rhinorrhœa attends *intracranial* application of radioactive isotopes we would point out that Evans et al.[5] recently reported that cerebrospinal rhinorrhœa developed in 5 of 45 patients treated by the transcranial insertion of ^{90}Y pellets into the pituitary fossa.

Our aim is the development of a simple, safe method of palliative treatment for patients with metastatic breast cancer. We feel that the theoretical advantages of high section of the stalk are outweighed by the relatively minor discomfort to the patient following radiation hypophysectomy by the screw technique.

A. P. M. FORREST
D. W. BLAIR
J. M. VALENTINE
A. T. SANDISON.

Western Infirmary and Regional Physics Department, Glasgow.

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2. Fraser, R., Joplin, G. F., Laws, J. W., Morrison, R., Steiner, R. E. *Lancet*, 1959, i, 382.
3. Forrest, A. P. M. *in* Cancer (edited by R. W. Raven); vol. VI. London, 1959.
4. Forrest, A. P. M., Blair, D. W., Valentine, J. M. *Lancet*, 1958, ii, 192.
5. Evans, J. P., Kelly, W. A., Harper, P. V. *Surg. Gynec. Obstet.* 1959, **108**, 393.

PITUITARY TUMOURS AFTER ADRENALECTOMY FOR CUSHING'S SYNDROME

SIR,—Dr. Montgomery and his coworkers (Oct. 31) described a patient in whom a pituitary tumour developed following adrenalectomy for Cushing's syndrome. They commented that it was hard to explain why she had no symptoms of Addison's disease in the presence of no functioning adrenal tissue. Her pigmentation and the assay for corticotrophin that Dr. Stack-Dunne made on her pituitary tumour suggest that she was secreting large amounts of corticotrophin. Corticotrophin in large doses has many extra-adrenal metabolic activities [1]; it is an interesting speculation that these activities may have made up for the loss of adrenal cortisol secretion.

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COAGULASE-NEGATIVE STAPHYLOCOCCI IN BLOOD-CULTURES

SIR,—Dr. Resnekov (Oct. 17) reported from this hospital 10 cases of subacute bacterial endocarditis following mitral valvotomy. In 9 of them coagulase-negative staphylococci were isolated from blood-cultures. Assessment of the significance of finding coagulase-negative staphylococci in blood-cultures is always difficult because of the presence of these organisms on human skin, and of the ease with which blood-cultures may become contaminated. It therefore seemed important to determine the frequency with which coagulase-negative staphylococci were isolated in blood-cultures from patients with other conditions, because it is against this background that the significance of Dr. Resnekov's findings has to be assessed.

The laboratory records for 1958, the year in which the majority of the investigations of Dr. Resnekov's patients were undertaken, showed that blood-cultures were made from 176 patients and that coagulase-negative staphylococci were isolated from 56. This material was analysed to allow comparison between the following three groups of patients:

Group I.—The 10 patients with subacute bacterial endocarditis following mitral valvotomy.

Group II.—56 surgical patients, from whom blood was taken within five minutes of endotracheal intubation. These blood-cultures were made during an investigation of the risk of bacteræmia after intubation.

Group III.—110 patients, who suffered from a variety of clinical conditions for which diagnostic blood-culture was requested.

The blood of the patients in groups I and III was usually collected by resident house-officers or medical students, and delivered into bottles containing "liquoid" broth. Three bottles were submitted to the laboratory on most occasions, and incubated respectively aerobically, anaerobically, and in an atmosphere containing 10% carbon dioxide. The bottles incubated anaerobically were kept for one to two weeks, and 2, 3 or 4 subcultures were made. The other two bottles were kept for six weeks, or until growth occurred, and subcultures on blood-agar plates were made at weekly intervals after the first week. The plates were incubated for twenty-four hours under the same conditions as the bottles. In group II, all

1. White, J. E., Engel, F. L. *J. clin. Invest.* 1958, **37**, 1556.

specimens were collected and the cultures handled throughout by the same person (I.J.)

The number of patients whose blood-cultures yielded coagulase-negative staphylococci is shown in table I. A distinction has been made between growth in any bottle at any stage of incubation and growth in all bottles within the first ten days. Blood samples were taken on two or more occasions from all the patients in group I, and from a small number of patients in group III, as shown in table II.

TABLE I—PATIENTS WITH BLOOD-CULTURES YIELDING COAGULASE-NEGATIVE STAPHYLOCOCCI

Group	Total patients	Coagulase-negative staphylococci	
		Total	All 3 bottles on first or second subculture
I	10	9	7
II	56	9	0
III	110	38	1
Total	176	56	8

TABLE II—BLOOD-CULTURES YIELDING COAGULASE-NEGATIVE STAPHYLOCOCCI

Group	Total blood samples	Coagulase-negative staphylococci	
		Total	All 3 bottles on first or second subculture
I	67	42	21
II	56	9	0
III	130	44	2

It is clear that there is a big difference in the incidence of coagulase-negative staphylococci between the patients with subacute bacterial endocarditis following mitral valvotomy (group I) and the patients in the other two groups. Not only were coagulase-negative staphylococci found more frequently but also the occasions when growth occurred in all 3 bottles on first or second subculture were practically limited to that group.

Staphylococci were found in 16% of the cultures from patients in group II and 33% of those in group III. This illustrates what is well known—namely, that special care in the collection of blood samples considerably reduces staphylococcal contamination, but it is unlikely that any form of skin disinfection can eliminate the risk of aspirating staphylococci in the deeper layers of the skin.

It is possible that if a quantitative estimation of the numbers of organisms in these blood samples had been made—e.g., by making pour plates [1]—many of the difficulties in assessing their role would have been overcome. Our results suggest that isolation of staphylococci from several culture bottles after a short incubation period indicates that the organism was probably present in the circulation. This probability is increased if the same result is obtained from further blood samples, as it was in 7 of Dr. Resnekov's post-valvotomy patients.

King's College Hospital Medical School, London, S.E.5. A. C. CUNLIFFE
I. JANOTA

ENDOCARDITIS AFTER MITRAL VALVOTOMY

SIR,—Dr. Resnekov strongly incriminates the surgeon's finger as a possible cause of postoperative staphylococcal endocarditis. He states that "the glove may be torn while splitting the valve" and suggests "putting a fingerstall of toughened rubber over the gloved finger" just before digital valvulotomy.

I have two comments. Firstly, even the usual glove over the surgeon's finger reduces his tactile accuracy as well as his chances of obtaining a satisfactory split of the commissures. The chances of a satisfactory split seem to be directly related to "restenosis" of the mitral valve. Secondly, although our surgeons have employed the bare finger for mitral commissurotomy for at least the past six years, our incidence of postoperative endocarditis is markedly lower in these patients than in our patients who have undergone aortic commissurotomy or repair of the various congenital defects where surgeons' gloves are used throughout the operation.

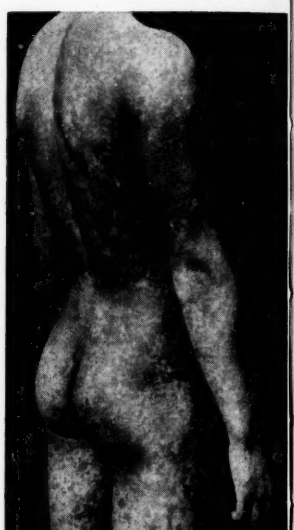
Robinette Foundation, Hospital of the University of Pennsylvania, Philadelphia. JOHN HELWIG.

1. Cunliffe, A. C., Gillam, G. G., Williams, R. *Lancet*, 1943, ii, 355.

EXANTHEM IN BRUCELLOSIS TREATED WITH NOVOBIOCIN

SIR,—In our hospital this year we treated 147 patients with brucellosis. In view of favourable reports of the effects of novobiocin on this disease,[1 2] we decided to use it in a group of 45 cases.

We gave 1·5 g. daily for ten days and 1 g. for five days. An acute exanthem developed in 24 cases (53%), appearing on the eighth day and lasting from two to fifteen days. Its appearance was maculopapular, morbilliform, urticariform, or scarlatiniform, and it was widespread and symmetrical (see figure). There was intense irritation and high fever (up to 40°C) in many cases, and in a few patients intense local œdema and slight erythema of the mucosæ developed as well. Antiallergic drugs and prednisone were of little or no value.



The characteristics of the œdema, such as its intensity, extent, and duration bore no relation to the dosage. Similarly, there was no connection between the presence or absence of œdema and dosage. The rash and the intense irritation and fever alarmed the patient, worsened his condition, and gave the doctor more to worry about than the illness itself.

We also had a patient in whom a hæmorrhagic diathesis, accompanied by hæmaturia, appeared at the same time as the exanthem.[3] In addition we often noticed yellow pigmentation of the mucosæ which, although well known, gave rise to confusion because on biochemical testing the serum gave the same positive reaction as bilirubin. The confusion was aggravated by the positive reaction given by some flocculation tests and by the hepatocellular jaundice produced by brucella.[4]

Digestive troubles were of less importance; although very frequent, they were not severe enough to oblige us to stop novobiocin.

We have not found novobiocin to be any more beneficial than other antibiotics in the treatment of brucellosis, either in immediate results or in avoiding relapses. A month after finishing the treatment of this group we had 18 relapses under hospital care (40%); so far we have had no news of the rest. Debono,[5] in Malta, has arrived at the same conclusion.

1. Torres Gost, J. *Rev. Cons. gen. Med. Esp.* 1958, **119**, 27.
2. Torres Gost, J. *Lancet*, 1958, i, 191.
3. Aznar Reig, A., López, A. *Medicina Madr.* (in the press).
4. Aznar Reig, A., López, A. *ibid.* (in the press).
5. Debono, J. E. *Lancet*, 1958, i, 585.

Because of these untoward reactions, and the lack of any demonstrable superiority over other antibiotics, we believe that novobiocin should not be used in brucellosis.

A. AZNAR REIG
Faculty of Medicine, Cadiz, Spain. ADRIANO LÓPEZ.

X-RAY EXAMINATION OF THE SCAPHOID

SIR,—I was interested to read Dr. Crawford's obervations (Oct. 31) concerning the visibility of scaphoid cracks on the initial X-ray films.

Some time ago, I approached this problem from the opposite angle. Typically, a patient is X-rayed soon after a wrist injury, with a suspected carpal fracture. A fine line is noted, usually near the middle of the scaphoid bone, especially when a magnifying glass is used. It is considered to be a " hair line " crack, and the wrist is put in plaster. In many cases, little or no change may be seen on subsequent X-rays, although a very slight difference in the positioning of the wrist, especially in the oblique view, results in an apparent change. The decalcification due to the immobilisation may also produce an apparent change.

Suspecting that some of these " hair-line " cracks might not be fractures at all, we X-rayed the scaphoid bones of about 100 uninjured patients, chosen at random. In at least one-third of these, a fine line could be seen running through the scaphoid bone, usually quite near its centre. Such a fine line, seen very soon after an injury, could easily be suspected of being a fracture.

My own experience, like that of Dr. Crawford, is that the great majority of scaphoid fractures are visible on the initial films. I would go further, however, and suggest that there is a danger in the other direction—namely, that of reporting as a " hair-line " crack, what is really a developmental or structural line.

There are of course exceptions both ways, and " safety first " is never a bad rule!

County Hospital, Hereford. PHILIP CLIFF.

PROCAINAMIDE AS A MUSCLE RELAXANT

SIR,—I have read with interest Dr. Phemister's letter (Nov. 7) concerning the use of procainamide as a muscle relaxant, and Dr. Forrester's letter (Nov. 21) suggesting that this action of procainamide might be due to " blockade of the small (gamma) motor efferents ". Dr. Forrester bases his suggestion on the similar pharmacological actions of procainamide and procaine hydrochloride; but, if this step is admissible, it seems unlikely that the mechanism of action he proposes is correct.

A tendon reflex is produced in response to the afferent discharge initiated by stretching the primary (annulo-spiral) endings of the muscle spindles. The intrafusal muscle-fibres, which are also contained within the muscle spindles, serve to modify the discharge of the primary endings to stretch. When, in conscious man, the gamma efferent discharge to the intrafusal muscle-fibres is reduced by a cinchocaine (' Nupercaine ') differential nerve-fibre block,[1] the tendon jerk may be completely abolished, as with procaine in the elegant cat experiments of Matthews and Rushworth [2] quoted by Dr. Forrester. Conversely, when the discharge along the gamma efferent nerve-fibres is increased—as is postulated to occur in man during reinforcement [3 4]—the tendon jerk is enhanced. Thus, examination of the tendon reflex under such controlled conditions as used in the experiments mentioned, may help in determining the level of intrafusal muscle-fibre activity at any instant. Under such conditions the intra-arterial infusion of procaine in various concentrations and total dosages failed to show any evidence of a selective " gamma blockade ".[1] As a result of experience with other drugs via the intra-arterial route, including decamethonium and tubocurarine, it appears that the gamma-efferent/intrafusal fibre neuromuscular junction is relatively resistant to blocking drugs.

In his letter Dr. Phemister stated that procainamide was of little benefit to patients with a spastic hemiparesis following a cerebrospinal accident. In this condition it does appear that there is an incorrect bias of the primary afferent endings of the muscle spindles due to increased gamma-fibre activity, [5] and on Dr. Forrester's hypothesis a more beneficial effect of procainamide might have been expected.

Finally, it must be noted that Dr. Phemister was concerned with the effects of procainamide on hypertonus, and, as stated elsewhere,[5 6] the reflex arcs subserving tone and tendon jerk are probably not identical. The experiments quoted above have all been concerned with the tendon jerk rather than with muscle tone, and as such do not help in explaining Dr. Phemister's results. However, as the experiments have tested the integrity of the small-fibre system (gamma efferents and intrafusal muscle-fibres) they do appear to indicate that Dr. Forrester's suggestion of a " gamma blockade " may not be the major factor in explaining Dr. Phemister's interesting observations.

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REFORM OF THE LAW ON HOMOSEXUALITY

SIR,—I should be very interested to learn how Sir Heneage Ogilvie supports his sweeping assertion (Nov. 21) that the " great majority " of doctors are opposed to the recommendations of the Wolfenden report. I suspect this to be one of the least substantiated claims to appear in your journal for a long while.

The only categorical statement that one can make in this respect about the great majority of doctors is that they are better fitted, because of their training, to consider the question of homosexual law reform than the great majority of other people.

Nobody likes the sight of a bad road accident, but a doctor, because his training enables him to control the upsurge of emotion and instinctive reaction which the circumstances arouse, is able to be helpful and efficient where another person, even if he knew what to do to help, might be quite unable to avoid being sick in a corner.

So it should be with accidents of the mind. Many people find the thought of homosexual behaviour extremely repugnant, but doctors at least should be able to consider the problem without being swayed by prejudice, or by the sort of emotionalism (. . . " loving husbands and happy fathers ") which colours Sir Heneage Ogilvie's letter. For this reason I say Mr. Kenneth Walker was right to raise this matter again in your columns, and to accuse us of professional apathy. Reform is needed, and the medical profession should not shirk its responsibility to press for that reform.

The tragic case of the Consett boy's suicide last month, which prompted Mr. Walker's letter of Oct. 31, is a difficult starting-point from which to argue the need for a change in the law. As Dr. Learoyd points out (Nov. 7), the case may well have been one of persistent sexual assault. Yet I believe it is the present attitude of the law towards young offenders which is most in need of reform. As things are now, a boy can be charged with offences committed with one or more boys of his own age where no question of assault exists. Such acts in adolescence are so common that they cannot reasonably be called abnormal. They are usually transitory and largely experimental, and are of little consequence unless blown up by the inevitable storm accompanying exposure.

Yet our legal system lumps boys who behave in this

1. Buller, A. J., Dornhorst, A. C. *J. Physiol.* 1959, **145**, 12P.
2. Matthews, P. B., Rushworth, G. *ibid.* 1957, **135**, 263.
3. Sommer, J. *Dtsch. Z. Nervenheilk.* 1940, **150**, 249.
4. Buller, A. J., Dornhorst, A. C. *Lancet*, 1957, ii, 1260.
5. Buller, A. J. *ibid.* p. 1262.
6. Buller, A. J. *Physiotherapy*, 1956, **42**, 203.

way together with criminals, and subjects them to the ponderous and unyielding process of the law designed to tackle crime. A boy charged with such an offence is brought to court, where the details of the offence are revealed with merciless legal accuracy in front of both the boy and his parents: the effect of this procedure on the boy can only be described as brutal.

One does not require a qualification in psychiatry to appreciate the emotional state of an immature mind following such an experience. Lacking the acquired insensitivity and emotional reserve of an adult, many boys in such circumstances suffer out of all proportion to the wrong they are deemed by law to have committed; and I know of one case where a serious attempt at suicide was made.

I sincerely urge all doctors to consider afresh whether the continued toleration of this state of affairs is compatible with the humanitarian principles of the profession.

Seaview,
Isle of Wight. M. B. REDDINGTON.

POSTCOITAL EXAMINATION OF SEMEN

SIR,—As MacLeod [1], a leading American seminologist, points out, even the experts cannot agree on what constitutes an abnormal spermatozoon or a normal count. For years 60 million spermatozoa per ml. was accepted as " normal ", but he believes that a count of 20 million per ml. is sufficient, with 40% motility. In his view the quality of the sperm movement is important.

Turley and Shaw,[2] reviewing 200 semen analyses and giving tentative support for pregnenolone therapy, express the same uncertainty: " When the voluminous articles on seminal inadequacy are reviewed there are controversies on the technique of semen analysis; there is inability to agree on normal and subnormal standards; and, worst of all, the many forms of therapy, the results of which are most discouraging." Barns et al.[3] found among sterility-clinic patients that there was no significant difference in subsequent pregnancy-rates between those who received some form of treatment and those who did not. Jeffcoate [4] similarly stressed that sterility work is merely investigatory and that we delude ourselves if we claim successes for treatment.

If this is so, it seems that an injustice has been done to those husbands who refuse to be examined by the conventional methods. They are often made to feel uncomfortably non-conformist, their intransigence occasionally leads to marital disharmony, and the doctor occasionally expresses himself in this wise: " If you do not cooperate in this investigation I shall not be able to help you." Is this strictly accurate? In similar vein, and in spite of their initial admission of nescience Turley and Shaw state the common view: " It should be emphasised that all specimens must be collected by masturbation or coitus interruptus."

As many husbands find these procedures an insuperable bar to investigation, attention is drawn to two alternative examinations. Neither of them gives such a precise report as the direct examination of the ejaculate, but it seems that this deficiency is not a matter of great moment provided an adequate diagnosis is made. These tests are a little more trouble for the clinician than the usual analysis, which places the onus on the patient and the pathologist.

The Sims (or Huhner) test was first described by Marion Sims about 100 years ago, and it should still be part of any investigation of male fertility, for in no other way can invasion of the cervical mucus by the spermatozoa be proved. Satisfactory results are found if the examination is made up to 4 hours after intercourse, but occasionally motile sperms are seen after 16 hours delay. The test should be timed to coincide with ovulation, when the cervical mucus is clear and transparent, and its relative freedom from leucocytes makes identification of the spermatozoa easy. With long artery forceps a drop of mucus is removed from the external os, placed on a microscope slide and immediately covered with a cover glass to prevent drying out. The motile cells can be located by low power, and then examined more accurately by high power. The motility is assessed (always a very personal estimation), and then the slide can be stained to determine the count and incidence of abnormal forms. In round figures, a count of 100 spermatozoa per high-power field with X 100 magnification is equivalent to a count of, say, 80 million per ml.

Failure to see any sperm cells necessitates a repeat examination, and a second failure suggests azoospermia, especially if testicular atrophy is found. The absence of the critical cells, however, may be due merely to the limitations of this indirect method, and the necessity of making a precise diagnosis without resorting to the unacceptable procedures has led to the use of a new method which has not been described elsewhere, but it has proved very satisfactory over several years. This is termed the postcoital urethral drainage specimen.

The patient is provided with a slide and cover glass, and, after a demonstration using water, he is instructed to place on the slide a few drops of the effluvium which remains in the urethra after the completion of normal intercourse. The cover glass is placed without delay and care is taken not to press on it during transit as this hastens drying out. It is taken to the rooms or laboratory, and motile spermatozoa are usually seen up to 4 hours after coitus. In azoospermia or oligospermia the presence of prostatic cells confirms the seminal origin of the fluid. The fact that the first part of the ejaculate contains the greatest density of sperm cells does not invalidate the test or diminish its usefulness, which is mainly to make a definite diagnosis of azoospermia.

These tests fail to give a full description of the ejaculate, the notable inadequacies of information being in volume, pH, viscosity, liquefaction, and total count. This incompleteness, however, is a matter of little practical importance since these factors are not alterable by " treatment ", nor are they of any concern to the patient in assessing the outlook. What is often lost sight of is that the whole purport of sterility work is to give a prognosis, which can be made only in rough terms: good, fair, or poor (never hopeless). Those in the first two categories are encouraged, within limits, to wait for pregnancy; those in the third are advised to adopt without delay. The two tests can give a prognosis with as much " accuracy " as the usual methods, without offending the moral standards of those patients whose sensibilities are often overlooked.

Auckland,
New Zealand. H. P. DUNN.

SURGICAL TREATMENT OF MITRAL STENOSIS

SIR,—We wish to draw attention to an error in our paper in last week's *Lancet*. In table v (p. 879) the percentage of deaths in the two series has been transposed. We regret this was not observed and led to a false conclusion in the summary, the relevant paragraph of which should read: "The operative mortality has been slightly lower (5% compared with 6·4%) and in addition more patients have been improved ".

ANDREW LOGAN
RICHARD TURNER.

Edinburgh.

1. MacLeod, J. *Amer. J. Obstet. Gynec.* 1955, **69**, 1256.
2. Turley, H. K., Shaw, J. L. *J. Urol.* 1957, **77**, 116.
3. Barns, T., Campbell, H., Snaith, L. *J. Obstet. Gynaec. Brit. Emp.* 1953, **60**, 670.
4. Jeffcoate, T. N. A. *ibid.* 1954, **61**, 181.

Parliament

The Hospital Service

IN opening this debate in the House of Lords on Nov. 19, Lord STONHAM said that the ordinary regional hospitals treated the overwhelming majority of sick people, and it was by the quality of their medical and nursing care that the hospital service as a whole stood or fell. He believed that their admittedly great achievements had been won by the people who worked in them in the face of relentless and blind opposition by the Treasury and by the bureaucracy of the Ministry of Health. It was a disgraceful story of exploitation and parsimony, because, despite a huge increase in the number of patients and in the demands of modern medicine, we were spending less in terms of real money today than before the war and our capital outlay was only half the pre-war level. The British Medical Association had said that we needed to spend £75 million a year on capital expenditure in our hospitals. This year we were spending £22 million, next year £25$^{1}/_{2}$ million, and in 1961–62 £31 million. Out of that £31 million, £15 million was to go to centrally financed major projects, £3 million to the replacement of obsolete equipment, such as boilers, leaving just over £11 million as capital allocation for all the hospitals in England and Wales. Yet half our hospitals were over seventy years old, war damage was virtually unrecompensed, and development had been virtually suspended over the past twenty years. It was intolerable that we paid more in profits to the manufacturers and wholesalers of National Health Service drugs than we spent on capital account for over 2500 hospitals with 400,000 beds and nearly 3 million patients a year.

He went on to point out that only 3·5% of the total spent on hospitals was spent on maintenance, which meant, for one thing, that we could not keep our hospitals clean. In some of the London hospitals which he knew wards had not been painted for twenty years. The regional boards had not the funds to achieve the minimum standards of cleanliness which could be enforced in a factory. Yet Whitehall sent out circulars demanding action on the dangers of cross-infection. In his group of hospitals in some wards fish-kettles were being used for sterilising equipment. To obtain equipment to sterilise by dry heat would cost £50,000 for the group. He did not doubt that the new major projects for hospital building were urgent and necessary, but were they more urgent than safety and cleanliness? He also appealed to the Government to give a fair deal to the ancillary non-medical staff. Their salary scales were low and their prospects poor. We should not continue to trade so shamefully on their devotion.

Those who ran our hospitals, he believed, were being frustrated by too much central control, too much paper work, and too many meetings. He would like to see the hospitals administered by a national board which should be given an adequate block grant and allowed to get on with the job.

Viscount WAVERLEY, in a maiden speech, said that one of the most important consequences of the National Health Service Act had been the development of the non-teaching regional hospitals and the diffusion of specialist skill. Inevitably this had meant that an ever greater proportion of patients was being treated at local hospitals instead of in the large teaching hospitals. This had led to overcrowding which reduced privacy, accentuated nursing difficulties, and facilitated cross-infection. In the special departments there were also shortages of technicians. The welfare of our patients and our reputation in the world of medicine increasingly depended on the way our provincial hospitals could acquit themselves. He agreed that the only way out of these difficulties was a massive programme of construction and reconstruction, but he also asked for an imaginative review of the conditions of service and rewards of nursing and ancillary staff.

Lord COHEN OF BIRKENHEAD stressed that though our hospitals were old we did now have a distribution of hospitals which was not dependent on charitable effort and a distribution of consultants which was dependent on the needs of the community and not on the ability to pay. But he believed that the service could be improved. The concept of the regionalisation of hospitals had not been fully realised. In many regions there was no contact between the regional hospitals and the teaching hospitals, and he suggested that the regions were too big and sprawling. There was a need for smaller regions, possibly with subregions in which there would be a central hospital under the influence of the teaching hospitals, and a regular interchange of staffs between teaching and regional hospitals. He would also like to see the place of the general practitioners in the hospital reconsidered.

He ended by asking whether we were using our hospitals to the best advantage. Were all our hospital beds really needed? When the N.H.S. was started the Ministry of Health suggested that for acute general hospitals 5 beds per 1000 of the population were needed. A recent investigation by the Nuffield Provincial Hospitals Trust suggested that this estimate was too high and that only 2·5 were needed. The investigation had shown that a third of the men and half of the women in a hospital in an industrial area were there not for medical, but largely for family, social, and economic reasons. The responsibility for these people should be not with the hospitals, but with the local authorities who should supply home helps and home nurses.

Lord GRENFELL turned the discussion to a part of the hospital service where there seems to be little doubt about the need for expansion—accommodation for mentally deficient children. He spoke especially of the needs of the Fountain Hospital in London which was built in 1893 in eight weeks with 384 beds for infectious diseases. Today it stood structurally almost as set up, but housed 600 children and had a waiting-list of 170. It was in the main corrugated iron huts of barrack-room type with wooden floorboards. There were no indoor recreation rooms, and in bad weather the beds had to be moved to the end of the wards to give the children space to play. Since 1920 plans had been put forward for a new hospital but had never materialised. It was now proposed that 300 of these children should eventually be moved to Queen Mary's Hospital, Carshalton. The Fountain was to be cut down to 100 beds. Yet with the waiting-list 770 beds were needed now. He asked the Minister what was to happen to the children who were not catered for.

Lord TAYLOR pointed out that we were spending less on our medical care than many other developed countries. Canada and France, for instance, spent 4·4% of their national income and we spent only 4%. He thought that we were getting our health services, and especially our hospital services, on the cheap. Moreover we were the only one of the developed countries where the proportion of national income devoted to health had actually fallen. He thought that the Government had been hypnotised by the gross figures.

In the past ten years a third of our schools had been rebuilt but only one new hospital completed. However much money we now spent on them it was important that we should get good value. At first there were bound to be mistakes and difficulties, for our architects lacked experience in hospital designing; and for this reason he especially welcomed the experimental work that had been done during these barren years by the Nuffield trusts. At present the two great defects of hospital building were control of cost and interminable delays while papers went to and fro from the Ministry of Health to the boards. He thought that the Ministry should advise, but not have to control or approve. It should delegate the job to the boards without the need to refer plans back for every little alteration.

Delays over day-to-day administration were also caused by the design of the service and the method of finance and control. Detailed parliamentary accountability led to grossly excessive recording and reference to higher levels. It was rule by circular and policy-making by returns. A further difficulty in administration was the multiplicity and size of committees. Hospital administrators spent most of their time servicing committees when they ought to be doing real work. The

trouble had arisen because there was confusion over representative and executive function. R.H.B.s and H.M.C.s were designed to be representative of all interests, but in fact they were executive bodies. The answer was to reduce their size to a maximum of 8 members and forbid the formation of sub-committees. To perform the representative function large advisory councils could be formed which might meet in plenary session, in public, for a couple of days once or twice a year for a grand inquest on the work of the committee or the board. Our hospital service was good, he ended, but not quite as good as it should be. The calibre of the staff was high but their enthusiasm needed to be rekindled. They needed quick decisions, freedom to decide, and enough money to do the essential jobs.

Lord ST. OSWALD, for the Government, suggested that it was pedantic to insist on the fact that only 1 new hospital had been built in the past twenty years without mentioning that 6 new hospitals were in extensive use, though further building remained to be completed. If as projects they had been less ambitious, they could be referred to now as completed hospitals. Work on another 9 hospitals was already in progress, building would start on 4 more in the next financial year, and yet another 11 were being planned.

A small design unit had been set up by the Ministry five years ago. It had already published a study on operating-theatres and was now studying nurses' homes, outpatient departments, and kitchens. The unit was being expanded, and in addition to writing bulletins it was to design hospital departments in different parts of the country. The first of these was to be an outpatient department at Walton Hospital, Liverpool. It was hoped that in this way the Ministry would be able to get to boards a great deal more information which they could use in preparing their plans.

The Government were giving the N.H.S. priority and importance during the present period of expansion and since 1954–55 (when it was 3·24) the percentage of the national product spent on the service in Great Britain had risen steadily. For 1958–59 it was estimated at 3·49.

Population (Statistics) Bill

In moving the second reading of this Bill on Nov. 12, Viscount HAILSHAM said that its main purposes were to make permanent the application of the Population Statistics Act of 1938 and to provide for obtaining information on causes of stillbirths for the whole of Britain by a certificate from a doctor or midwife stating the cause of death and the estimated duration of pregnancy. The Bill also made small alterations in the particulars required on the registration of birth or of death. The most important of these changes were that the age of the father, as well as the age of the mother, should be stated in the registration of birth, and that a separate category of divorced was added to the three existing categories on the registration of death.

At present, both in Scotland and in England doctors and midwives provided certificates of stillbirth, but in England and Wales these certificates certified only that the child had not been born alive, whereas in Scotland they gave the cause of the birth not having been a live birth. Under the Bill the cause would now also be given in England and Wales, and Scottish certificates would introduce the present English practice of giving the duration of pregnancy. Information from this register was not open to the public and was available only at the discretion of the Registrar General. The information was required because it was considered desirable to obtain more statistical data which could shed light on the causes of stillbirths. Infant mortality had been declining steadily in this country in recent years, but the decline was largely due to a reduction in the mortality of children aged between one week and one year. Mortality of children in the first week of life had not declined as rapidly, nor had the stillbirth-rate shown much variation. Moreover, statistics established what at first sight was a close and significant connection between the causes of early infant deaths in the first week of life and the causes of stillbirths, which the Bill would now make available.

Lord TAYLOR was fascinated by the inquiry as to the age of the father. Was there any *a priori* evidence of declining fertility in the male? What had led the Registrar General to require this particular piece of information?

Viscount HAILSHAM explained that the age of the father was required because medical research was more interested now than previously in the question of human mutations. It was interesting to know whether, or to what extent, the age of the father might affect the rate of mutation in the human being, because it enabled one to hazard some kind of opinion as to the effect of radioactivity upon human mutations. Although it was bound to take some time to build up any significant statistics about anything so small as the proportion of mutational births, it was now considered sufficiently significant and relevant to be included in the questions asked.

Supplementary Professions

It is nearly nine years since the Cope Committees on Medical Auxiliaries reported.[1] Their recommendations form the basis of the Professions Supplementary to Medicine Bill which the Minister of Health introduced on Nov. 18.

The Bill seeks to provide machinery for the registration of chiropodists, dietitians, medical-laboratory technicians, occupational therapists, physiotherapists, radiographers, remedial gymnasts, and speech therapists and for regulating their professional education and conduct. For each profession it is proposed to set up a board (of from 11 to 17 members) which will be responsible for the maintenance of its register, and approval of courses of training, qualifications, and institutions. Only someone who is on one of these professional registers will be entitled to use the title of, for example, State-registered chiropodist or State-registered dietitian. The medical profession will be represented on each board by 3–6 members. Each board will have disciplinary powers.

A council will also be set up, to be called the Council for Professions Supplementary to Medicine, to coordinate and supervise the activities of the boards. The Council will have 23 members, including 2 doctors appointed by the Health Ministers, 1 representative of each of the English Colleges, 2 representatives of the Scottish Corporations, and 1 representative of the General Medical Council.

There will be a right of appeal from disciplinary decisions of the boards and Council to the Privy Council. Subject to this body's approval, new boards may be set up, and old boards abolished or amalgamated, provided the total number does not exceed 12.

Shortage of School Dentists

On the adjournment on Nov. 23 Mr. NORMAN DODDS spoke of the unsatisfactory situation of the school dental service. He suggested not only that it had deteriorated since 1955, but that because of the growing age of the dentists in the service (267 under thirty, 404 over fifty) there would soon be a big wastage.

In his reply Mr. KENNETH THOMPSON, the parliamentary secretary to the Ministry of Health, said that there were not enough dentists in the general dental service and we had not been able to attract from that limited pool enough dentists to provide for the needs of the school service. But the figures showed a progressive, very slow increase (1008 dentists in 1956, 1032 in 1959). He agreed that the increased age of these officers raised a problem which we must face in the not very distant future. To some extent it was being met, or the position was being held, by an increase in the number of sessions which outside dentists are prepared to give.

There were, he was sorry to say, only 17 hygienists in the school dental service, but there were 1140 full-time chairside assistants. When some courses which were just about to start were under way 40 hygienists would be trained in the first year, and 60 dental ancillaries would be taken into the new course at the London Hospital when the premises were ready for use.

1. See *Lancet*, 1951, i, 895, 904.

The expansion in the dental schools recommended by the McNair Committee could not take place overnight. 2 new dental hospitals were at present under way, expansion was going on or being planned in 6 others. It was also proposed that there should be a new dental hospital as part of the new Cardiff teaching hospital.

QUESTION TIME

Dental Ancillaries

Miss JENNIE LEE asked the Minister of Health how many dental nurses were being trained. Mr. WALKER-SMITH replied: I assume the hon. Member has in mind the dental ancillaries for whom the General Dental Council is undertaking an experimental training scheme. Preparations for this are well advanced and it is intended that the first two-year training course will begin next autumn. Miss LEE: Is the Minister aware that he is 50% understaffed in school dentists and that he should be thinking of a very much larger scheme than he has in mind and should be speeding it up more quickly? Mr. WALKER-SMITH: I thought that my answer was very encouraging indeed. It shows that we are getting on with the work of training the dental ancillaries. The question of the provision of dentists is another matter.

Miss LEE: Can the Minister give the number now being trained? Mr. WALKER-SMITH: The training centre for dental ancillaries being built at the New Cross General Hospital will provide for an annual intake of 60 students. In addition, there are the dental hygienists, for whom we are also making training arrangements. Mr. ANEURIN BEVAN: Can the Minister really express satisfaction at the progress which has been made when in 1959 he is only now building the training colleges and facilities for ancillary dentists and hygienists, although this was started ten years ago?

Obituary

HAROLD WILLIAM WILSON

M.S. Lond., F.R.C.S.

Mr. Harold Wilson, whose death we announced last week, was appointed to the staff of St. Bartholomew's Hospital in 1918, and for some ten years was the hospital's senior surgeon.

He was born at Carlisle in 1880 and qualified from Barts in 1903. After holding house-appointments there he took the F.R.C.S. in 1905. Later, as demonstrator of anatomy in the Medical College, he established a reputation as a teacher, and he obtained the M.S. degree in 1909. During the 1914–18 war he served in France with the R.A.M.C.

He was appointed to the staff of the Royal Cancer Hospital and the Victoria Hospital for Children, but he gave up both these appointments soon after he became an assistant surgeon at his own hospital in 1918. He became full surgeon in 1928 and senior surgeon in 1936. In the late war he served in the E.M.S., at first at the sector hospital at St. Albans, and later at the hospital in the City. Here, with his junior colleagues, he was responsible for the treatment of the many air-raid casualties which came to the hospital, mostly at night, during the bombing of 1940–41, as well as for routine surgical duties and teaching. His retirement from the active staff was delayed for four years by the war till 1946 and he was then appointed consulting surgeon and a governor of the hospital.

He went eagerly to the delightful home in Suffolk which he had built overlooking the marsh at Haddiscoe soon after the 1914–18 war, and where he had passed much of his leisure. His plans for retirement were never realised, for his wife died soon afterwards, but the visits of his only daughter with his grandchildren, and the surroundings which he loved so well, meant much to him in his declining years. He died on Nov. 14.

J. E. A. O'C. writes:

"Harold Wilson was a fine general surgeon, and his diagnostic skill, sound judgment, and careful technique gave excellent results. Among his special interests were urology, abdominal surgery, and the treatment of fractures. As a teacher, he was outstanding. Students were attracted by the quiet voice and carefully reasoned arguments, and his ward-rounds and lectures left a lasting impression. His house-surgeons and chief assistants gained from the example which he set them of gentleness at all times, careful operating, and conscientiousness. The nurses in his wards also became devoted to him, with the result that the surgical firm of which he took charge in 1928 remained, in the opinion of many, until its disruption at the outbreak of war, the outstanding one in the hospital. Perhaps because he was never physically robust he wrote little, and rarely attended surgical meetings. Despite this, his contributions as a teacher in his own hospital were considerable.

"To one who knew him during the last twenty-five years, he leaves many memories—of his thin, upright figure always so carefully dressed, usually in country tweeds; of the delightful hospitality at his London and country homes; of his excellence as a shot; of the pleasure he derived from his garden, and particularly the memory of a quiet man who was unfailingly gentle in his relationships with everyone."

ERIC STEPHEN GURNEY HORNING

M.A. Oxon., D.Sc. Melb.

Dr. E. S. Horning, professor of experimental pathology (histology) in the University of London, at the Chester Beatty Research Institute, died on Nov. 14 at the age of 59.

Born and educated in Sydney, he contrived to see service with the Australian Imperial Forces in Flanders during the 1914–18 war, though under age. Afterwards he took his degree in the honours school of comparative anatomy and zoology at Oxford. He began his research career under Prof. W. E. Agar, F.R.S., at the University of Melbourne. Horning took the D.SC. of that university in 1928. Two years later he was awarded a Rockefeller fellowship, and he worked with Dr. Albert Fischer at the Kaiser Wilhelm Institute for Experimental Medicine in Berlin-Dahlem, at other European research centres, and in the United States with Dr. E. V. Cowdry at Washington University Medical School, St. Louis. In 1933 he came to London and joined the staff of the Imperial Cancer Research Fund as Beit fellow.

On the outbreak of the late war he received a commission in the Royal Air Force, and afterwards graduated from the Royal Naval College, Greenwich, to serve with the Navy in Iceland, the South Atlantic Station, and the Far East, and with the Royal Indian Navy, as lieut.-commander, R.N.V.R. In 1947, he accepted a readership in experimental pathology in the University of London, at the Chester Beatty Research Institute, and was accorded the title of professor in the same subject in 1956. During the Korean war he once more wished to leave his scientific life to serve, and he was only with difficulty dissuaded.

His early papers (several ahead of their time) were much concerned with the nature of the mitochondria in protozoa (*Paramœcium*, *Opalina*) and in other material—their orientation in the cytoplasm, relation to the nucleus, and their structure and enzymatic function. Other studies dealt with the Golgi apparatus, the process of dedifferentiation in tissue culture, the application of the technique of micro-incineration to the histochemistry of normal and malignant cells, and the cytopathology of morphine

poisoning. Very numerous later contributions dealt with the endocrinology of cancer and carcinogenesis, with which he became specially identified.

His papers on this subject dealt with the hormonal relation between the ovary and the adrenal gland and its significance in mammary cancer, the production in mice of pituitary tumours by œstrin, and of glandular carcinomas of the prostate, and the influence of œstrogens on the lymphoid tissues. Many were brought together in his book, with the late Harold Burrows, *Œstrogens and Neoplasia* (1952), and in various notable reviews, particularly one jointly with F. Bielschowsky.[1] Another series of papers described the induction of pulmonary and other tumours in mice from subcutaneous grafts impregnated with methylcholanthrene. Even with increasing interests he remained devoted to questions of endocrine carcinogenesis—for example, the histogenesis of the œstrogen-induced renal tumours of the male hamster. Latterly he was engrossed with the mechanism of action of plastic films in evoking sarcomata on implantation subcutaneously; and had recently made a fine study of the rodent tumours which can be induced with iron-dextran.

A. H. writes:

"In all his work Eric Horning applied the highest standards, as an excellent operator and experimentalist, and as a superb histologist with complete command of the most elegant technique. But when all has been said of his scientific contribution, there still far more remains the man. Unusually endowed with qualities of character and the heart, his main mark was generosity, which was bestowed very kindly and quietly upon all, but especially upon those who needed it most. It was part of his nature that he enjoyed the savour of life to the full, had the happiest memories, and had accumulated a great fund of stories, grave and gay, scientific, human and romantic, which were the delight of his friends. He was a sterling colleague and confidant, and countless people in every walk of life are richer for knowing him, and strengthened by a gay and undying example."

HUGH BASIL GREAVES NEWHAM

M.D. Durh., M.R.C.P., D.P.H., D.T.M. & H.

Dr. Newham, formerly director of the museum and warden of studies at the London School of Hygiene and Tropical Medicine, died on Nov. 11.

He was born at Winslow, Bucks, where his father practised for many years as a family doctor. He was educated at Wellingborough and Malvern. After qualifying in medicine from St. Thomas's Hospital in 1898 he gained much varied clinical experience in the Far East and in British Guiana. He was attracted to the then newly, and tardily, recognised specialty of tropical diseases, and in 1906 he joined the old London School of Tropical Medicine at the Royal Albert Dock, West Ham.

The following year he was made demonstrator under Patrick Manson, and more immediately under C. W. Daniels, whose close friend and right-hand man he quickly became, and whom he succeeded as director of the school and superintendent of the hospital in 1910. Newham at once showed himself a first-rate administrator and an outstandingly successful teacher. He gave the main course of instruction at the school on the clinical pathology of tropical diseases. In the 1914–18 war he served as consultant in tropical diseases in East Africa, and in camps, hospitals, and autopsy huts in Uganda, Kenya, and Tanganyika he gained fresh stores of knowledge to enrich his discourses at the school.

Administration and teaching left him little time for original research, but his careful investigation of the histological changes in the human liver induced by infestation with the fluke *Clonorchis sinensis* were valuable. In 1920 the school left the Albert Dock region to become a part of the School of Hygiene and Tropical Medicine in Bloomsbury and Newham's unabated energies shifted from the teaching of clinical pathology to the organisation of the school's museum and demonstration material. He retired in 1938 to Suffolk, and gave his still unflagging energy to archæology, helping in many local "digs".

H. M. H., recalling the time he worked with Newham while the school was still at West Ham, writes:

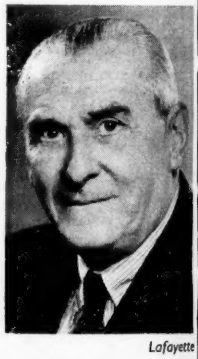
"It was difficult, indeed wearisome, to get at it by road or rail, but once reached there was a reward. And so students came from the far corners of the tropics till, in Newham's day, there were over sixty to a session. The medical wards of the hospital, roomy, bright, cheerful, were always more than half-filled with Chinese, Indian, West Indian, and African seafaring patients. Newham was tall, handsome, well built, spare and energetic. His resonant voice and clear exact diction expressed in simple, well-ordered phrases the thoughts of his forceful, well-stocked mind. He held the attention of his class, especially in his remarkable lectures on hæmatology, by his evident affection for his subject. He was sociable, helpful, and apparently always in good humour and his popularity was great and deserved."

JOSEPH FRANCIS ENGLEDUE PRIDEAUX

Kt., C.B.E., M.R.C.S.

Sir Francis Prideaux, whose death on Nov. 15 we announced last week, was director-general of the Ministry of Pensions medical service from 1947 to 1949.

He was born in 1884, the son of Dr. Engledue Prideaux of Wellington, Somerset, and educated at Epsom College and University College Hospital. Soon after he qualified in 1908 he joined the Colonial Service, and from 1909 to 1916 he was stationed in Fiji. On his return to England he joined the R.A.M.C. His work among cases of so-called "shell shock" turned his interest to psychiatry. He was doing research work at Cambridge when in 1921 he was asked to join the staff of the new Ministry of Pensions to help to undertake a diagnostic survey of the many cases of neurasthenia with which the Ministry had to deal.



Lafayette

During his years at the Ministry he took an interest in the reablement of the physically as well as the mentally disabled. In 1936 he was appointed a member of the Delevingne Committee. At the beginning of the late war he was appointed director of the Ministry's medical services with charge of its hospital service, and in this post he did much to encourage the formation of the successful paraplegic unit at Stoke Mandeville Hospital.

C. G. M. writes:

"The death of Sir Francis Prideaux, following so closely on that of Sir Walter Haward, marks the passing of an epoch in medical service to the war disabled. To these two men, who reached the summit of their special sphere of medical administration, must go the main credit for a policy of medical treatment, rehabilitation, and assessment of disablement which has in many respects proved a model for the world. To the clinical side of this achievement Prideaux particularly made a great contribution, critically evaluating in the inter-war years the medical performance in the first world war. It was during this time, and as a result of this work, that Prideaux laid the foundation of his later success and was led to formulate a policy for pensions administration in the second war already looming in Europe. In this policy he received the support of most of the medical thinkers of the day, with the resulting disapprobation of that anomaly 'shell-shock' as a clinical entity. When the first casualties of the late war arrived in England Prideaux had his plans ready for their treatment at the hospitals

1. *Brit. med. Bull*, 1958, **14**, 106.

administered by the Ministry of Pensions. 'Rehabilitation' was the slogan, and with the invaluable cooperation of other Government departments the seriously incapacitated found themselves unexpectedly fitted for employment in industry. In the famous medical centres like Roehampton and Stoke Mandeville Prideaux has many monuments to his memory.

"By his colleagues he will be remembered and deeply respected for his kindness, sound judgment, alertness of mind, and unyielding attitude when medical principles were being improperly assailed, and most of all as an outstanding administrator who still remained a good doctor."

In 1941 Prideaux was appointed O.B.E. and he was promoted to C.B.E. in 1946. On his retirement in 1949 he was created a knight bachelor. He leaves a widow and two daughters.

THOMAS GIBSON

M.D. Edin., D.P.H.

Dr. Thomas Gibson, who was the first full-time medical officer of health for Wakefield, died on Nov. 3 at the age of 88.

He was educated at Alloa Academy and the University of Edinburgh, where he qualified in 1895. After holding a house-appointment at the Camberwell Infirmary he spent three years as assistant medical officer of the borough and port of Southampton.

In 1903 he was appointed medical officer of health for Wakefield, a post he held for 33 years.

Of his work there, his successor, C. G. K. T., writes:

"Thomas Gibson left me a great legacy of good work to carry on in Wakefield. His annual reports, which start on Feb. 24, 1904, are a joy to read because of their impeccable English, and because of the perspicacity and sheer wisdom of the advice which he gives to his committee. His greatest work, I think, was the advice to deal with tuberculous patients in their own homes. To that end he had twenty-six houses built in 1922—special houses which are still used for tuberculous patients. His love for children is shown by his report to the schools in 1908 or 1909, describing the appalling conditions under which children went to school in those days, particularly in wet weather. He paints a picture of children sitting without their jackets on, round the fire, while their jackets dry. He persuaded the city council to raise a fund for clogs for poor children, so that they could go to school with dry feet at least. When he came to Wakefield, the infant-mortality rate was 200 per 1000, and through his influence a health visitor was appointed, who carried on pioneer work with babies and mothers, and in 1906 founded the Babies' Welcome, the first organisation of its kind in the country, which was a provident society, encouraging mothers to save up for their confinements, supplying clothing and food to necessitous mothers, and helping them in many other ways. When Wakefield decided to apply for the Corporation Act in 1924, Dr. Gibson, with prophetic foresight, obtained powers to prohibit persons in advanced stages of tuberculosis from handling food. Food-poisoning was made for the first time in this country a notifiable condition.

"Dr. Gibson is remembered by many, and I pay my tribute to one I consider a great, humble man who did a hard job of work as well as he possibly could."

In 1939 Dr. Gibson gladly came out of retirement to help during the war. He served as an assistant M.O.H. at Weymouth and later at Torquay, where he continued to work in the active practice of public health till he was 80. He retired to Somerset, and though in his later years he had many physical infirmities, his cheerfulness was undaunted and his intelligence unimpaired, and he continued to take a keen interest in public health, literature, natural history, and antiquities. Dr. Gibson, who had been a widower for ten years, leaves two sons (one of whom is a doctor) and a daughter.

Diary of the Week

NOV. 29 TO DEC. 5

Monday, 30th

UNIVERSITY COLLEGE, Gower Street, W.C.1
5 P.M. Prof. E. P. Kennedy (Chicago): Biosynthesis of Complex Lipids. (First of two lectures.)
POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Prof. Sheila Sherlock: Hepatic Coma.
UNIVERSITY OF ST. ANDREWS
4 P.M. (Department of Medicine, Queen's College, Dundee.) Mr. John Grieve: Physiology of the Urethra.

Tuesday, 1st

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. J. L. Gowans: The Lymphocyte.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. E. H. Belcher: Measurement of Red Cell Life Span.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Mr. G. L. Bourne: Anatomy and Physiology of the Amnion and Chorion.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. R. H. Marten: The Sweat Retention Syndrome.
ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Dr. R. B. McConnell: Role of Heredity in Gastrointestinal Disorders.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Dr. Henry Miller: Accident Neurosis.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology department, Queen's College, Dundee.) Dr. H. G. Morgan: Methods of Investigation of Diseases in Bone.

Wednesday, 2nd

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.15 P.M. *History of Medicine*. Prof. Ian Richmond: Roman Military Hospitals.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Prof. G. M. Wilson: Acute Nutritional Changes in Disease.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Histopathology of Fungous Diseases.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. N. R. Barrett: Surgery of Pulmonary Tuberculosis.
MIDLAND MEDICAL SOCIETY
8.15 P.M. (36, Harborne Road, Edgbaston, Birmingham, 15.) Prof. C. H. Stuart-Harris: Recognition, Diagnosis, and Treatment of Virus Diseases.
MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) *Medicine*. Dr. J. Hoenig: Shibboleths in Psychosomatic Medicine.
UNIVERSITY OF ST. ANDREWS
2.30 P.M. (Department of Medicine, Queen's College, Dundee.) Prof. J. L. Henderson: Aspects of Physiology in the Newborn.

Thursday, 3rd

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Dr. H. G. H. Richards: Problems in Bone Marrow Diagnosis. (Erasmus Wilson demonstration.)
5.30 P.M. Mr. Barrett: Hiatus Hernia. (Otolaryngology lecture.)
ROYAL SOCIETY OF MEDICINE
5 P.M. (United Services.) Prof. R. F. Woolmer, Surgeon Lieutenant J. Cox: Artificial Respiration.
8 P.M. *Neurology*. Dr. Hugh Garland, Sir George Pickering, Prof. R. H. S. Thompson: Neurological Complications of Diabetes.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dame Janet Vaughan: Relation of Radiation Dose to Radiation Damage.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. T. Alper, Dr. M. Ebert, Dr. R. H. Thomlinson: Biological Effects of Radiation.
NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Orthopædic Hospital, Oxford
8.30 P.M. Prof. Joseph Trueta: Reflections After Ten Years in the Oxford Chair of Orthopædic Surgery.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology department, Queen's College, Dundee.) Mr. H. J. Seddon: Paralytic Poliomyelitis.

Friday, 4th

ROYAL SOCIETY OF MEDICINE
10.30 A.M. *Otology*. Dr. Mary Barber, Dr. Peter Walford, Mr. J. H. Otty: Use and Abuse of Antibacterial Drugs in Otology.
5.30 P.M. *Anæsthetics*. Dr. Leon Kaufman: Anæsthesia and Dystrophia Myotonia. Dr. H. J. Poppelbaum: Rediscovery of Air for Controlled Ventilation in Thoracic Surgery.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. Ronald Belsey: Reconstruction of the Œsophagus.
4 P.M. Prof. K. W. Donald: Hæmodynamics in Common Heart-diseases.
HEBERDEN SOCIETY
2.15 P.M. (Wellcome Foundation, Euston Road, N.W.1.) Opening of two-day meeting.
PLYMOUTH MEDICAL SOCIETY
8.30 P.M. (Freedom Fields.) Dr. Denis Hill: Psychophysiology of Murder.

Saturday, 5th

MIDLAND THORACIC SOCIETY
3 P.M. (36, Harborne Road, Edgbaston, Birmingham, 15.) Mr. S. J. MacHale: Thoughts on Surgical Treatment. (Presidential address.)

Births, Marriages, Deaths

BIRTHS

LEWES.—On Nov. 14, at Bedford General Hospital, North Wing, to Daphne (née Wailes) and David Lewes, D.M., M.R.C.P.—a son, John Steel, a brother to Joanna, Virginia, Jane, and Bryony.

Notes and News

RACIAL SEGREGATION IN BLOOD-TRANSFUSION

AT a recent meeting of the American Association of Blood Banks,[1] three physicians of Columbia University, New York, suggested that blood-transfusion would be safer if donor and recipient were always of the same race. Their reason is not that any blood-group is peculiar to one race, but that some groups are commoner in one race than in another. Thus group A is commoner, and group B less common, in white Americans than in American Negroes; and (more important, since they are not routinely tested for in all centres) the Kell, Kidd, and Duffy factors vary in frequency: in America 12% of whites are Kell-positive and 2% of Negroes; 77% of whites are Kidd-positive and 93% of Negroes; 68% of whites are Duffy-positive, and 26% of Negroes. Thus a Negro transfused with blood untested for the Kell factor will be six times as likely to be sensitised by positive blood if the donor is white than if he is Negro. The proposal was strongly criticised by several at the meeting, on the ground that racial differences in blood-group are less important than individual differences; in any individual case only complete testing, including cross-matching, will ensure safe transfusion.

University of Oxford

On Nov. 14 the following degrees were conferred:

D.M.—Marcia I. P. Wilkinson.
B.M.—J. A. G. Emery, M. A. Gibson (in absentia).

University of London

The following have passed the final examination for the degrees of M.B., B.S.:

Honours.—R. T. J. Allen (*e*), University College; R. A. C. Davies (*d*), London; A. D. Dayan (*a*, *b*), London; T. H. Foley (*b*), St. Thomas's; J. R. Garrett (*e*), King's College; Brian Greenwood (*d*), St. Thomas's; Brenda E. Higgs (*d*), Royal Free; D. J. Holdstock (*a*), University College; M. J. H. Homewood (*b*, *d*, *University Medal*), London; Gillian A. Jonas (*c*), St. Mary's; D. J. Tooby (*d*), St. Bartholomew's.

(*a*) distinguished in pathology; (*b*) distinguished in medicine; (*c*) distinguished in applied pharmacology and therapeutics; (*d*) distinguished in surgery; (*e*) distinguished in obstetrics and gynæcology.

Pass.—Babatunde Kwaku Adadevoh, Joshua Adeyemi Adebusoye, Evelyn M. Adey, P. M. Aichroth, J. G. Allardice, Ethel M. M. Allen, E. R. W. Ashley, Nancy E. Atkins, Ann M. Atkinson, Howard Baderman, R. V. V. Baker, P. J. Banfield, R. B. Barnbrook, Anne P. Barrett, J. G. Bass, C. L. Bayliss, M. R. Beck, D. R. Benady, Derek Berzon, Ved Bhushan Bhardwaj, J. M. Black, Muriel Blackburn, C. G. Boateng, R. P. Bonner-Morgan, Patricia M. Booth, M. R. Boundy, K. M. Bridgman, Brenda M. Brookes, A. A. Y. Brouet, Brian Burbidge, P. E. Burke, W. H. Butler, J. M. Campbell, G. N. Cash, Rosemary J. Chambers, Marion R. Chaplin, Elizabeth J. Chilcott, T. Chimele Okoro Chiori, C. E. P. Clarke, A. B. Clymo, Ann R. Coe, J. C. Collings, G. I. Collins, J. T. Cooke, C. P. Cooper, T. A. R. Cox, P. J. Coyle, Patrica L. Crawford, Anita E. Davies, Ann Davies, C. F. Davies, David Davies, Olwen M. S. Davies, Patricia M. Dean, P. J. De Buse, Gisele M. M. de Lane Lea, A. S. Denfield, J. L. C. Dobson, Margaret R. Dockray, Shirley P. Duke, J. F. Dunne, K. R. Durrant, G. S. Dymond, Diana A. M. Ernaelsteen, David Fergie-Woods, June R. Finer, R. F. M. Forward, G. C. Fox, G. G. Francis, T. I. Francis, P. S. Franks, E. N. Gleave, M. R. Gooding, N. M. Goodwin, A. M. Gould, Eric Gowland, G. J. K. Greenlaw, R. J. Gregory, I. P. Griffith, R. F. Gunstone, T. R. Hailstone, D. A. Hay, Lydia M. Hayes, M. R. Hendry, Ann J. Hill, D. J. Hill, Elizabeth J. Hiller, J. R. Hoare, Ann Hodgson, L. A. Holbrook, Kenneth Hollinrake, R. G. Holmes, D. F. Hopkins, Rita J. Hornik, M. J. K. Hudson, Bertram Igbogbahaka, S. E. Inman, Oluyinka S. Itayemi, Edith B. A. Iver, F. H. A. Jago, M. J. Jameson, I. C. Johnson, Josephine I. Johnston, I. W. Jones, M. T. Jones, D. W. Kay, T. R. M. Keeble, Moira B. Kelly, B. N. C. Kempton, J. H. Kendall, Robert King, Marion E. Knighton, P. A. Knowlson, F. W. Knox, Eva M. Kohner, D. G. Kraft-Goddard, David Lamb, K. L. Lancer, R. S. Lane, J. W. Latham, B. H. Latimer, P. A. Lawrence, R. A. Lee, D. A. Leigh, R. G. M. Letcher, K. J. B. Lewin, P. K. Lewin, Phyllis S. Lewis, Ruth D. Low, Gertrude Lowith, A. N. McClean, D. I. McCuaig, R. S. McFarlane, P. A. J. M. MacFaul, Ingrid J. McGovern, A. J. Mackenzie, Helen M. McG. McNie, B. W. Maitland, Ninian Marshall, R. D. Marshall, Patricia A. Martin-Turner, Ann S. Mason, Susan Y. Mearman, C. C. Merry, R. H. S. Mindham, John Monkman, V. M. E. Montegriffo, C. A. Morris, L. W. Morrish, G. W. Moxon, Belinda J. Myles, M. J. Nicholls, J. C. Oakley, Norah M. P. O'Hanlon, J. Olatunde Oluwasanmi, R. B. F. Orr, T. J. Owen, Janet E. Page, Rosemary F. McL. Page, W. J. C. Parker, Ann Parry-Williams, Ronald Paul, A. J. Pearce, D. J. Peebles, Shirley A. Peppitt, G. M. Peters, J. B. Phillips, E. N. Pickering, Janet A. Pinner, J. D. C. Plant, C. P. Roberts, J. C. Roberts, J. S. Robinson, Ann T. Roden, J. W. Rollins, D. W. Ross, C. J. Rowland, Helen Rubens, Gerald Sackstein, Peter Saywood, Shirley A. M. Schofield, J. McL. Singleton, Aldona J. Sito, Jane Skinner, A. E. Slater, M. E. Smith, P. W. J. Smyth, P. G. Soutter, Jean M. M. Steadman, R. A. Stockwell, M. J. Streule, Ronald Stubbings, K. J. Sugden, J. C. Swann, N. H. L. Taylor, Bethan Thomas, D. G. Thomerson, M. J. A. Thompson, S. H. Thompson, Anne U. Tothill, John Townsend, Barbara W. Truscoe, Sarosh Dhunjishaw Vakil, Zarina Iqbal Ramzan Vellani, Anna Warrender, J. R. L. Westaway, Annette A. Whitaker, J. E. White, Ann Whitfield, A. L. J. Williams, Barbara J. Willmer, A. B. Wilson, M. B. Wilson, R. D. Winch, M. C. Winterton, C. C. Wise, J. G. Woolich, M. C. Wotton, William Yen, P. M. E. Youngman.

1. *New York Times*, Nov. 15, 1959.

University of Cambridge

On Nov. 14 the degree of M.D. was conferred on H. R. Mallows.

University of Bristol

The following appointments have been made:

Dr. G. W. Burton, lecturer in anæsthetics; Dr. K. T. Evans, clinical teacher in radiodiagnosis; Dr. K. R. Gough, research fellow in medicine.

University of Leeds

Dr. P. G. F. Nixon has been appointed lecturer (in cardio-respiratory problems) in the department of medicine.

University of Sheffield

Dr. T. E. Gumpert has been appointed lecturer in cardiology.

University of Aberdeen

Dr. P. V. Best has been appointed lecturer in pathology.

British Association of Pædiatric Surgeons

The annual general meeting of this association will be held from July 6 to 8 at the Hospital for Sick Children, Great Ormond Street, London, W.C.1. Further particulars may be had from Mr. R. B. Zachary, the Children's Hospital, Western Bank, Sheffield, 10.

Mental Health at Home and Abroad

The National Association for Mental Health will hold a conference on this subject on Thursday and Friday, March 24 and 25, at Church House, Westminster, S.W.1. Further particulars may be had from the conference secretary at the association, 39, Queen Anne Street, W.1.

Lord Adrian will give the Romanes lecture of Oxford University in 1960.

On Monday, Dec. 7, at 8.15 P.M., at Marlborough Day Hospital, 38, Marlborough Place, London, N.W.8, Dr. Felix Post will speak on affective disorders of the elderly.

Mr. A. B. L. Clarke, O.B.E., has been appointed secretary of the Imperial Cancer Research Fund and will have his office at 49, Lincoln's Inn Fields, London, W.C.2. Mr. Kennedy Cassels, who has been the Fund's secretary for the past 21 years, will now give the whole of his time to the affairs of the Royal College of Surgeons.

Sir Harry Platt has left for a tour of Latin America which is sponsored by the British Council. He will represent the United Kingdom at the congress of the Latin American Society of Orthopædics and Traumatology in Chile, and he will also visit Peru and Colombia.

Dr. Hugh Wallace is visiting Sudan and Ethiopia, and Dr. B. G. B. Lucas, Argentina, under the auspices of the British Council.

Dr. Kenneth Bergin has been elected master of the Guild of Air Pilots and Air Navigators for 1959–60.

The second edition of the World Health Organisation's annotated list of *Current Indexing and Abstracting Journals* has been published as supplement no. 2 to *Library News*, 1959, vol. 12.

CORRIGENDUM: *Treatment of Galactosæmia.*—In the letter by Dr. Payne and his colleagues (Nov. 14) the quantities of galactose-1-phosphate in red cells were μ mols. per ml. and not μg. per ml.

Appointments

CAROTHERS, J. C. D., M.B. Lond., D.P.M.: consultant psychiatrist, St. James' Hospital, Portsmouth.
DAVIES, J. C., M.B. Durh.: assistant physician (S.H.M.O.), geriatrics, Newcastle upon Tyne group of hospitals.
FRANCE, ELIZABETH M., M.B. Lond., F.F.A. R.C.S., D.A.: part-time consultant anæsthetist, Elizabeth Garrett Anderson Hospital, London.

East Anglian Regional Hospital Board:

BHATTACHARYYA, M. B., M.B., B.SC. Calcutta, M.R.C.P.E.: medical registrar, Peterborough hospital group.
GUYER, P. B., M.B. Lond.: medical registrar, Ipswich and East Suffolk Hospital.
PATON, S. L., M.B. Edin., F.R.C.S.: senior casualty officer, Peterborough Memorial Hospital.

Colonial Appointments:

BRICK, T. D., M.B. Dubl., D.M.R.D.: radiologist (diagnostic), Hong Kong.
COHEN, F. E. P., M.D., D.T.M. & H.: district M.O. and medical superintendent, Leeward Islands.
HADDOW, I. F. G., M.B. Birm.: M.O., Hong Kong.
MCILWAINE, C. L. K., M.B. Edin.: M.O., South Pacific health service.
PALMER, J. W. B., M.B. Cantab.: M.O., Hong Kong.
PERRY, J. G., M.B. Lond.: M.O., Kenya.
WILKINS, R. D., F.R.C.S.: surgeon specialist, Jamaica.